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### Economic impact of medication nonadherence by disease groups: a systematic review

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Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A literature search was conducted in PubMed and Scopus in March 2017 where neither publication date nor language restriction filters were used. Seventy four individual studies assessing the cost of medication nonadherence were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Individual studies reported a wide range of costs, calculated using different methods. Disease groups assessed were cardiovascular disease, mental health, diabetes mellitus, osteoporosis, respiratory disease, gastrointestinal disease, epilepsy, HIV/AIDS, Parkinson’s disease, musculoskeletal conditions, cancer, addiction, metabolic conditions and blood related conditions. Medication possession ratio was the metric most utilized to calculate patient adherence, but the cut-off points chosen to define nonadherence varied. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (81% of studies), pharmacy costs (72%), inpatient costs (51%), outpatient costs (51%), emergency department visit costs (30%), medical costs (27%) and hospitalization costs (18%). Lower levels of adherence were generally associated with higher total costs. The annual adjusted disease state specific economic cost of nonadherence per person ranged from $949-$53,504 (in 2015 US dollars). Costs attributed to “all causes” nonadherence ranged from $5,271 to $52,341.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. However, current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy and change due to significant variations in costs and their economic implications. Differences in methods make the comparison amongst studies challenging and make an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338
Strengths and Limitations of this study:

- This is the first systematic review assessing the economic impact of medication nonadherence across all disease groups.
- The findings of this review build on current literature and present the first comprehensive analysis of the cost ranges of medication nonadherence within and amongst disease groups whilst simultaneously analyzing the range of outcomes used to estimate costs.
- A large proportion of studies provided insufficient statistical data and considerable heterogeneity to perform a meta-analysis according to outcome/indicators.
- Owing to heterogeneous research design, examination of the economic impact of medication nonadherence was restricted due to the lack of full economic evaluations available.
1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources. [2]. Medications are a cost-effective treatment modality, but intentional and unintentional inappropriate medication use by patients is common, mostly through differing degrees of adherence termed medication nonadherence. Medication adherence is defined as ‘the extent to which the patients’ behavior matches agreed recommendations from the prescriber’, emphasising the importance on the patients’ decisions and highlighting the modifiable aspect of nonadherence[3].

With estimates of 50% nonadherence to long term therapy for chronic illnesses[4], efforts to improve medication adherence represent an opportunity to improve health outcomes and health system efficiency. The clinical, economic and human consequences of medication nonadherence pose significant burdens. Estimates of the costs range from US$100-$290 billion[5] in the United States, €1.25 billion[6] in Europe and approximately A$7 billion[7-8] in Australia. As well as substantially increasing healthcare costs, nonadherence compromises the effective use of medicines, can decrease patients’ quality of life, increases the risk of medication misadventures, can lead to poor health outcomes, and can result in preventable hospitalizations[9]. Nonadherence is thus a critical clinical and economic problem [4].

An understanding of the economic impact of medication nonadherence on the healthcare system can influence health policy. While the cost of nonadherence for some disease groups has already been analyzed with varying findings, no systematic reviews provide a holistic and comparative picture across disease groups. The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.
2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[10].

2.1 Search strategy and selection criteria

A literature search was conducted in March 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB]) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases. Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[11] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-
group analysis and statistical significance), conclusions and miscellaneous (funding source, references to other relevant studies, limitations and reviewers comments).

All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [12], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[12]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The cost analysis of studies (figures 2 and 3) reported annual medication nonadherence costs incurred by the patient from a healthcare provider perspective. The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. The most utilized methods were medication possession ratio (MPR) and proportion of days covered (PDC). Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [13]. All studies were classified in accordance with Drummond’s distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis).

The Drummond checklist [14] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as
high quality if at least 75% of Drummond’s criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

Outcome/indicator costs were independently extracted utilising predesigned data extraction forms (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs, emergency department costs, and hospitalisation costs) for the purpose of integrating the findings on the cost of medication nonadherence to pool data and increase the power of analysis.
3 Results

3.1 Study Selection

Search strategies retrieved 2691 potential articles after duplicates were removed. Two hundred and sixty six articles were selected for full text review. Seventy four studies were included in the review (Figure 1).

Figure 1: Flow diagram of references identified, retrieved and included in the systematic review
3.2 Characteristics of individual studies

Sixty-one studies (82%) were conducted in the United States[15-75], four in Europe[76-79], four in Asia[80-83], three in Canada[84-86], one in the United Kingdom[87] and one across multiple countries throughout Europe and the United Kingdom[88]. Publication years ranged from 1997 to 2016. Individual studies reported a large variety of costs, calculated by varying means. Forty-one studies (55%) reported unadjusted costs[15 19 20 23 25-29 31-36 39 41-43 45-49 51 56-59 61 62 66 69 75 77-79 81-83 88], 19 (25%) adjusted costs[16-18 22 24 37 44 50 52-54 60 65 67 70-72 76 80], 11 a combination of adjusted and unadjusted[21 30 38 40 55 63 64 68 73 74 86], two unadjusted and predicted[84 85] and one predicted costs[87]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy claims data (87%)[15-22 24-45 48 50 52-77 81-86]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data, disease state specific recommended guidelines and health claims data. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 48 studies (64%) reporting nonadherence based on this measure[17 18 21 22 25-29 33-37 39 40 42-44 48 50 51 53-57 61-72 75-77 81-86]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g. 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (9%)[24 30 38 41 45 73 74], with all other studies utilizing an array of measures including self-report[87], urine testing[49], observational assessment[88], time to discontinuation[52], cumulative possession ratio[16], disease specific medication management guidelines[59 78], Morisky 4-Item scale[46], medication gaps[31], prescription refill rates[15 20] and medication supplies[60]. The main characteristics of the included studies are summarised in eTable 1.
3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high [26 30 33 43 44 50 65 69 76 82], 55 of medium [15-19 21-25 27-29 31 32 34-41 46-49 51 52 54-57 59-61 63 64 66 67 70-75 77 78 80 83-88] and nine of low quality [20 42 53 58 62 68 79 81]. Scores ranged from 26.1% to 87.5% (mean 62.9%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [65]. The item ‘the choice of discount rate is stated and justified’ was applicable only to studies covering a time period of more than one year; all studies that cover more than one year failed to identify or explain why costs had not been discounted. Details of the analysis and interpretation of results were lacking in the majority of studies resulting in medium or low quality scores.

Through utilisation of Drummond’s distinguishing characteristics of healthcare evaluations criteria [13] it is apparent that no full economic evaluation was conducted in any of the included studies. All studies performed partial economic evaluations of varying extents. The classification of economic evaluations resulted in 54 cost description studies (72% of those included), 15 cost outcome descriptions and five cost analysis studies (eTable 1).
3.4 Medication nonadherence and costs

The adjusted total cost of nonadherence across all disease groups ranged from $949 to $53,504, while the unadjusted total cost ranged from $669 to $162,699. Figures 2 and 3 highlight the minimum, maximum and interquartile range of annual costs incurred by patients across disease groups where three or more studies were included for review. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 2: Annual Adjusted Medication Nonadherence Costs
*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.
** All cause costs: mixed disease state studies
Many different indicators were used to estimate medication nonadherence costs. The main ones were total cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (47%), medical costs (29%), emergency department costs (28%), and hospitalization costs (18%) (eTable 1).

Lower levels of adherence across all measures (e.g. MPR, PDC) were generally associated with higher total costs. From those that reported total or total healthcare costs, 37 studies (50%) reported nonadherence costs to be greater than adherence costs\cite{17 18 20 22 24 25 30-32 35 36 40 42 43 48 49 51 54-58 64-79 85-88} and 11 studies (15%) reported nonadherence costs to be less than adherence costs\cite{16 19 29 37 52 56 75 81 83 84}. Four reported fluctuating findings based on varying nonadherence cost subcategories\cite{26 41 61 82} and two studies reported conflicting findings between adjusted and unadjusted costs \cite{73 74}. Sunyecz et al\cite{62}, Eisenberg et al\cite{34} and Joe et al\cite{80} reported all cause total nonadherence costs to be higher ($28,395 vs. $24,134, $7,551 vs. $7,051 and $5,271 vs. $4,375) but disease group specific nonadherence costs to be lower ($1923 vs. $3273, $703 vs. $1012 and $3,252 vs. $4,151) whereas Hansen et al\cite{40} reported all cause total...
nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

The association between nonadherence and cost was determined through use of a variety of scaling systems. The most utilized methods were MPR and PDC. These measures could then further be subcategorized based on the percentage of adherence/nonadherence. The 80-100% category was classified as the most adherent group across both scales, with the most common definition of nonadherence being <80% MPR or PDC.

**Cardiovascular Disease**

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [17 24 54 58 60 61 70 75 82 84 85]. Six studies reported adjusted costs [17 24 54 55 60 70] with annual costs being extrapolated for two of these[24 54]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs\textsuperscript{16,20,21,23,25}, medical costs\textsuperscript{15,16,20, 23,25} and outpatient costs\textsuperscript{16, 21}. The annual economic cost of nonadherence ranged from $3,347 to $19,472. Sokol et al[60] evaluated the economic impact of medication nonadherence across three cardiovascular conditions; hypertension, hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined, pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups. Total costs and medical costs were lower for the adherent groups of hypertension and hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups. Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total costs of nonadherence ranging from $1,433 to $8,377 [58 61 75 82 84 85]. Rizzo et al[58] reported cost findings through subgroup analysis of five conditions. For all conditions the total healthcare costs were higher for nonadherent groups compared with adherent. While Zhao et al[75], categorized participants into adherence subgroups; finding that total healthcare costs were lower for the nonadherent population. The remaining studies used five key indicators to determine the economic impact: inpatient costs[61 82], outpatient costs[61 82], pharmacy costs[61 84 85], medical costs[84 85] and hospitalization costs[84 85].

**Mental Health**

The analyses used to report the economic impact of medication nonadherence in mental health varied widely. Ten of 13 studies provided a total nonadherence cost estimate in mental health[16 18...
20 45 52 59 67 80 87 88], with annual cost data being extrapolated for three of these[20 59 88]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from $3,252 to $19,363 [16 18 52 53 67 80]. Bagalman et al[18] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs – while all other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication nonadherence were pharmacy costs[16 32 45 52 53 59 67 80], inpatient costs[32 53 59 87 88], outpatient costs[16 32 52 88] and hospitalization costs[15 16 52 88].

The total unadjusted cost for medication nonadherence ranged from $2,512 to $18,811 as reported in three studies[45 59 88]. Becker et al[20] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%, <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al[87] outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

**Diabetes mellitus:**

Nine studies reported some cost measurement of the impact of medication nonadherence with reference to the health system and the individual[33 38 40 44 68 70 81 83 86]. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion[44]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819 [40 44 68 70 86]. One study reported total costs in relation to subgroup analysis based on MPR level[68], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients[70].

A further three studies reported unadjusted cost findings[33 81 83] and four studies reported unadjusted costs in addition to adjusted values[38 40 68 86]. Unadjusted total healthcare costs and/or total costs ranged from $1,142 to $7,951. Extrapolated annual costs were determined for two studies based on cost data presented [33 83].

The most prominent indicators used to determine costs were pharmacy costs[33 38 40 68 70 86], outpatient costs[33 40 70 83 86], inpatient costs[40 70 86] and hospitalization costs[44 81 83]. All studies assessed the direct costs associated with medication nonadherence. One study evaluated
the relationship between nonadherence and short term disability costs in addition to assessing
direct costs[38].

**Osteoporosis:**

The cost of medication nonadherence in relation to osteoporosis was predominately examined
through analysis of the direct costs associated with nonadherence using total healthcare costs
and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department
costs. Two studies further assessed the economic impact of nonadherence through evaluation of
fracture related costs [41 77]. Four out of 11 studies reported the adjusted cost of medication
nonadherence in addition to reporting unadjusted costs [21 73 74 76]. Three studies further
classified nonadherence through subgroup analysis, with Briesacher et al[21] using MPR 20% interval
increases and the two studies conducted by Zhao et al[73 74] using PDC, with ≥80% classified as high
adherence, 50-79% medium adherence and <50% low adherence . In the studies conducted by Zhao
et al[73 74], total healthcare costs were highest for the medium adherence group ($41,402 and
$44,190) followed by the highest adherence group ($37,553 and $43,863), and lowest for the low
adherence group ($34,019 and $43,771). These annual costs were extrapolated from study data. In
contrast, Briesacher et al[21] modelled the subgroup analyses against the lowest adherence group
(<20% MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from $669
to $43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In
the three studies that reported the lowest level of nonadherence to be PDC <50%, the cost of this
category ranged from $16,938 to $43,404 [41 73 74].

One study examined only the medical costs of nonadherence through MPR subgroup analysis in
commercial and Medicare supplemental populations. The findings were that, for all levels of
nonadherence, costs of nonadherence were higher for Medicare supplemental patients [39].

**Respiratory Disease:**

All five studies reported the unadjusted cost of medication nonadherence. The methods of
classifying adherence levels varied greatly among them[29 31 46 57 78]. Two studies used MPR[29
57], one the Morisky 4-Item scale[46], one the Global Initiative for Chronic Obstructive Lung Disease
(GOLD) 2007 Guidelines[78] and one a 37 day gap in claims data[31]. Joshi et al[46] reported on the
indirect costs of medication nonadherence through consideration of losses in total productivity
costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs.
Delea et al[29] reported a direct relationship between decreases in medication nonadherence level

and total costs, whereas Quittner et al.[57] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the lowest subgroup of adherence across all measures ranged from $804 to $36,259.

**Gastrointestinal Disease:**

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [37 50 65]. Of these, two reported the total cost ($12,085 and $37,151)[37 65] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs[23 47]. Carter et al.[23] reported hospitalization costs to be $42,854 while Kane et al[47] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

**Epilepsy:**

Three studies reported the economic impact of medication nonadherence in epilepsy. They all reported unadjusted costs using an MPR cut off of <80%[28 35 36]. The main economic indicators used to assess total costs were inpatient costs ($2,289 to $6,874), emergency department visit costs ($331 to $669) and pharmacy costs ($442 to $1,067). Davis et al[28] modelled the costs of the nonadherent group against the adherent group. The annual costs reported by Faught et al[36] were extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from $1,866 to $22,673.

**HIV/AIDS:**

The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all three studies was similar [19 25 56]. Two of the three studies examined the costs only for HIV[19 25], while Pruitt et al[56] assessed the cost in AIDS as well as HIV. The total unadjusted costs for nonadherent HIV patients ranged from $16,957 to $30,068 with one study further categorizing patients with HIV as having either a high viral load or low viral load[19]. The total cost of nonadherence in AIDS was $30,523[56]. All studies used comparable indicators (total cost, inpatient cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
**Parkinson’s Disease:**

The direct costs associated with Parkinson’s disease were assessed in all three studies. The unadjusted total cost ranged from $10,988 to $52,023 [27 30 66]. Wei et al[66] further sub grouped patients into MPR adherence percentage categories, and found that costs increased on all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that $10,290 could be attributed to medication nonadherence annually[30].

**Musculoskeletal Conditions:**

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence[43], one assessed only the medical costs[63] and one examined the direct costs in commercial and Medicare supplemental patient populations[72]. Zhao et al[72] reported the adjusted annual cost in the commercial population to be $22,609, and in the Medicare supplemental group, $28,126. Ivanova et al[43] reported only unadjusted costs and the annual total cost of $3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

**Cancer:**

Two studies evaluated the effects of medication nonadherence in cancer[26 69]. One study reported total annual costs of $119,416[69], while the other gave a subgroup analysis based on classified adherence levels[26]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs ($162,699 and $67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

**Addiction:**

The adjusted annual total healthcare cost of medication nonadherence was reported as $53,504[49] while the unadjusted cost ranged from $29,406 to $52,213 [49 64]. Leider et al[49] reported the main contributors to this cost to be outpatient costs ($10,829) and pharmacy costs ($8,855), whereas Tkacz et al[64] reported them to be inpatient costs ($28,873 and $28,407) and outpatient costs ($15,893 and $15,460).
Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of $138,525[48]. The economic indicators used to derive this cost were inpatient costs ($16,192), outpatient costs ($111,100), emergency department visit costs ($801) and pharmacy costs ($3,538).

Blood conditions:

Only Candrilli et al[22] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of $13,458 for nonadherence classified as MPR <80%.

All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[24 40 43 54 57 59 88]. Ten studies reported on economic indicators without giving total cost or total healthcare cost[15 38 39 47 48 53 75 79 88], and one study reported on costs per episode of nonadherence[79].

The adjusted cost of medication nonadherence was reported in 10 studies with an estimated range of $7,808 to $52,341 [22 24 30 40 52 54 60 65 70 71]. Sokol et al[60] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[54] reported only using MPR level breakdown.

Fourteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of $1,037 to $53,793 [15 34 39 43 47 48 51 57-59 62 75 79 88]. A further four studies reported adjusted and unadjusted costs[30 38 40 86]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).
3.5 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of required statistical parameters in particular standard deviation[89]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.
4 Discussion

To our knowledge, this is the first systematic review analyzing the economic impact of medication nonadherence across different disease groups. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, Emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesise costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g. mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g. cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to medication nonadherence thus enabling greater planning in terms of health policy to help counteract costs.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [90], who compared six key adherence measures on the same study participants, found that the measures produced similar adherence values for all participants, although PDC and continuous measure of medication gaps produced slightly lower values. While this highlights the comparability of the measures of
medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 64% of studies, followed by PDC, which was used in 9%. These percentages were consistent with those found recently by Sattler et al [91]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[84] defined MPR as the total days’ supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[70] removed the number of hospitalized days from the calculation; and Pittman et al[54] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Twenty-eight studies defined nonadherence as MPR< 80%, and 19 studies categorized nonadherence into varying percentage subgroups. While Karve et al[92] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent hospitalizations in patients across a broad array of chronic diseases, 71 of the 74 studies included in this review examined more than just hospitalization costs as an indicator metric. Further research is required to identify and standardize nonadherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 74 studies covered, 30 different indicators were used to measure the cost of nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardized approach be established to measure and report the economic impact of medication nonadherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of nonadherence cost that is attributable to each outcome to determine an appropriate model[93]. The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future research.

Many studies have examined the relationship between nonadherence and economic outcomes using a cross-sectional analysis[44]. The implications of this are that potentially crucial confounders such
as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

None of the studies included a full economic evaluation. An economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each[13]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasised the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[94] highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[15 16 58 67 68 87]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.
5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However, differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilisation of existing data could help to better define costs and provide valuable input into the development of an economic model to standardise the economic impact of medication nonadherence.
6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data extraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

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Competing interests: None declared

Data sharing statement: All data from systematic review available in paper and supplementary material.

Acknowledgement: RC research is supported by an Australian Government Research Training Program Scholarship.


<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Objective</th>
<th>Study Characteristics</th>
<th>Adherence (as reported in paper)</th>
<th>Outcomes/Indicators</th>
<th>Results (USD, 2015)</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
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</table>
angiotensin receptor blockers.

Dragomir et al\[4\]
2010 Canada
To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalization costs.

**Design:** Retrospective cohort study
**Follow Up:** 3 years
**Sample Size:** 56896 (A:38217, NA:18679)

**Measure:** MPR
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent

**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted and predicted
**Classification:** disease state specific and hospitalised patients

**Currency Year:** CAD, 2006
**Cost of Nonadherence:** Unadjusted
- Disease state specific: THC:$7165 ($6900.87), PC: $1800 ($1733.64), MC: $1370 ($1319.50), HC: $3995 ($3847.73)
- Unadjusted Hospitalised patients:
  - THC: $17397 ($16755.67), PC: $2685 ($2586.02), MC: $2608 ($2511.86), HC: $12104 ($11657.79)
  - Predicted disease state specific: HC:$3877 ($3734.08)
  - Predicted hospitalised patient: HC:$11715 ($11283.13)

**Quality:** medium
**Classification:** cost description

Dragomir et al\[5\]
2010 Canada
To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.

**Design:** Retrospective cohort study
**Follow Up:** 3 years
**Sample Size:** 55134 (A:28549, NA:26585)

**Measure:** MPR
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent

**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted and predicted
**Classification:** disease state specific and hospitalised patients

**Currency Year:** CAD, 2005
**Cost of Nonadherence:** Unadjusted
- Disease state specific: THC:$6243 ($6175.76), PC:$2506 ($2479.01), MC:$1241 ($1227.63), HC:$2496 ($2469.12)
- Unadjusted Hospitalised patients:
  - THC: $14725 ($14566.40), PC: $3374 ($3337.66), MC: $2475 ($2448.34), HC: $8876 ($8780.40)
  - Predicted disease state specific:
Pittman et al[6]
2011 US
To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.

Design: Retrospective cohort study
Follow Up: 18 months
Sample Size: 381422
(A:258013, MA:65795, LA:57614)

Measure: MPR
Classification:
MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence
Method of Assessment:
pharmacy claims data

Total Healthcare Costs
Pharmacy Costs
Medical Costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2009
Cost of Nonadherence: all cause:
THC(>80):$6798.67 ($7505.66), THC(60-79):$7072.67 ($7808.16), THC(<59):$7401.33 ($8170.99),
MC(>80):$4472.67 ($4937.78), MC(60-79):$4840.67 ($5344.05), MC(<59):$5138.67 ($5673.04)
Disease state specific:
PC(>80):$558.67 ($616.77), PC(60-79):$442.67 ($488.70), PC(<59):$325.33 ($359.16),
MC(>80):$1596.67 ($1762.71), MC(60-79):$1722 ($1901.07), MC(<59):$1792.67 ($1979.09)

Quality: medium
Classification: cost description

Pittman et al[7]
2010 US
To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and

Design: Retrospective cohort study
Follow Up: 2 years

Measure: MPR
Classification:
MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence

Total Healthcare Costs
Outpatient Costs
ED Costs
Pharmacy Costs
Hospitalization

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence: Adjusted:
THC(>80):$7261 ($8077.79),
THC(60-79):$7530 ($8377.05),
THC(<59):$7370 ($8199.05),
OC(>80):$3390 ($3771.34),
OC(60-79):$3705 ($4121.77),

Quality: medium
Classification: cost description
To investigate variations in compliance with four classes of antihypertensive agents—diuretics, ACEIs, CCBs and \( \beta \)-blockers.

**Design**: Retrospective cohort study

**Follow Up**: 12 months

**Sample Size**: 7211 (P:2668, NC:3101, NP:649, T:793)

**Measure**: ordinary least square regression analysis

**Classification**: >80% = persistent, ≥30<80% = non-compliance, <30% non-compliance

**Total Healthcare Costs**

<table>
<thead>
<tr>
<th>Type of Costs: unadjusted</th>
<th>Classification: all cause and disease state specific</th>
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<td>TH(&gt;80): $7182 ($7989.90)</td>
<td>THC(&gt;80): $7560 ($8410.42)</td>
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<td>EDC(&lt;59): $172 ($191.35)</td>
<td>THC(&lt;59): $694 ($1037.26),</td>
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<td>ODC(&lt;59): $3887 ($4324.25)</td>
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<td>THC(30-80): $694 ($1037.26),</td>
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<td>EDC(&gt;80): $102 ($113.47)</td>
<td>PC(&lt;59): $1880 ($2091.48)</td>
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<td>EDC(60-79): $131 ($145.74)</td>
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<td>PC(&gt;80): $2317 ($2577.64)</td>
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<td>THC(30-80): $694 ($1037.26),</td>
</tr>
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**Quality**: low

**Classification**: cost description
blockers and the health care costs associated with various degrees of compliance. = non-persistence

Method of Assessment:
pharmacy claims data

| THC(>80): $2135 ($3190.98), THC(30-80): $2488 ($3718.58), THC(<30): $2529 ($3779.86), Acute MI: THC(>80): $1358 ($2029.67), THC(30-80): $1711 ($2557.27), THC(<30): $1752 ($2618.55) |


To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study
Follow Up: 12 months
Sample Size: 137277

Measure: medication supply
Classification: 1-19%, 20-39%, 40-59%, 60-79%, 80-100%
Method of Assessment:
pharmacy claims data

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 1998
Cost of Nonadherence: All cause: Diabetes:
TC(1-19): $16498 ($23071.58), TC(20-39): $13077 ($18287.49), TC(40-59): $12978 ($18149.05), TC(60-79): $11484 ($16059.77), TC(80-100): $8886 ($12426.60), PC(1-19): $1312 ($1834.76),
Hypercholesterolemia:

Hypertension:
TC(1-19): $9747 ($13630.66),
TC(20-39): $11238 ($15715.75),
TC(40-59): $9491 ($13272.66),
TC(60-79): $8929 ($12486.73),
TC(80-100): $8386 ($11272.38),
PC(1-19): $916 ($1280.98),
PC(20-39): $952 ($1331.32),
PC(40-59): $1123 ($1570.46),
PC(60-79): $1271 ($1777.43),
PC(80-100): $1817 ($2540.98),
MC(1-19): $8831 ($12349.69),
MC(20-39): $10286 ($14384.43),
MC(40-59): $8368 ($11702.20),
MC(60-79): $7658 ($10709.31),
MC(80-100): $6570 ($9187.80),

Hypercholesterolemia:
TC(1-19): $10916 ($15265.45),
TC(20-39): $7982 ($11162.40),
TC(40-59): $6756 ($9447.91),
TC(60-79): $8412 ($11763.74),
TC(80-100): $6752 ($9442.31),
PC(1-19): $1067 ($1492.14),
PC(20-39): $1152 ($1611.01),
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<td>$8867</td>
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<td>$1972</td>
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<td>20-39</td>
<td>$4124</td>
<td>$1736</td>
<td>$5509</td>
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<tr>
<td>40-59</td>
<td>$6522</td>
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<tr>
<td>80-100</td>
<td>$4570</td>
<td>$6830</td>
<td>$6676</td>
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</tbody>
</table>

Disease state specific: Diabetes

<table>
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<tr>
<th>Age Group</th>
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<th>PC Costs</th>
<th>MC Costs</th>
</tr>
</thead>
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23456789101112131415161718192021222324252627282930313233343536373839404142434445464748495051525354555657585960

Page 38 of 80
Design: Retrospective cohort study  
**Follow Up:** 3.3 years  
**Sample Size:** 15206 (not specified)  

**Measures:**  
- **MPR Classification:**  
  - MPR<80 = undersupply, MPR >120 = oversupply  
  - Total Healthcare Costs  
  - Inpatient Costs  
  - Outpatient Costs  
  - Pharmacy Costs  

**Type of Costs:** unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2002  
**Cost of Nonadherence:**  
- **THC:** $6032.5 ($7830.11), **IC:** $2067 ($2682.94), **OC:** $3965 ($5146.52), **PC:** $130 ($1683.74)

**Quality:** medium  
**Classification:** cost description

---

Stroupe et al[10]  
2006  
US  
To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patients with complicated and uncomplicated hypertension and to
examine the association of refill adherence with hospitalization and healthcare costs among these patients.

To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.


- **Design:** Retrospective cohort study
- **Follow Up:** 1 year
- **Sample Size:** 1705 (A:624, NA:1081)

**Measure:** MPR
- **Classification:** MPR≥80 = adherent, MPR <80 = nonadherent

**Method of Assessment:** pharmacy claims data

<table>
<thead>
<tr>
<th>Total Healthcare Costs</th>
<th>Pharmacy Costs</th>
<th>Medical Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Costs:</strong> adjusted</td>
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<tr>
<td><strong>Classification:</strong> all cause and disease state specific</td>
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</tr>
<tr>
<td><strong>Currency Year:</strong> USD, 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cost of Nonadherence:</strong> all cause: THC:$17807 ($21370.30), PC:$4915 ($5898.52) MC:$12892 ($15471.77)</td>
<td></td>
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</tr>
<tr>
<td><strong>Disease state specific:</strong> THC:$2789 ($3347.10), PC:$489 ($586.85) MC:$2300 ($2760.25)</td>
<td></td>
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</tr>
</tbody>
</table>

Zhao et al [12] 2014 US

- **Design:** Retrospective cohort study
- **Follow Up:** 1 year

**Measure:** MPR
- **Classification:** <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%

**Method of Assessment:** pharmacy claims data, census data

<table>
<thead>
<tr>
<th>Total Healthcare Costs</th>
<th>Pharmacy Costs</th>
<th>Medical Costs</th>
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<tbody>
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<td><strong>Classification:</strong> all cause and disease state specific</td>
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<tr>
<td><strong>Currency Year:</strong> USD, 2010</td>
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<tr>
<td><strong>Cost of Nonadherence:</strong> all cause: PC(96-100):$2976.80 ($3247.04), PC(90-95):$2826.99 ($3083.63), PC(85-89):$2795.39 ($3049.16), PC(80-84):$2690.89 ($2935.17), PC(70-79):$2192.83 ($2391.90), PC(60-69):$2323.27 ($2534.18), PC(40-59):$2153.93 ($2349.47), PC(&lt;40):$1749.18 ($1907.97)</td>
<td></td>
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<tr>
<td><strong>Disease state specific:</strong> THC(96-100):$6536.05 ($7129.40), THC(90-95):$6493.80 ($7083.31),</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mental Health

Bagalman et al.[13]

2010

US

To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.

Design: Retrospective cohort study

Follow Up: 1 year

Sample Size: 1258

(A:444, NA:814)

Measure: MPR

Classification:

MPR≥80 = adherent, MPR <80 = nonadherent

Method of Assessment: pharmacy claims data

Total Costs:

Type of Costs: adjusted

Classification: disease state specific

Currency Year: USD, 2005

Cost of Nonadherence:

TC:$6894 ($8273.53), STDC:$2134 ($2561.03), WCC:$762 ($914.48), PTOC:$3998 ($4798.03)

Quality: medium

Classification: cost description

THC(85-89):$6459.40 ($7045.79),

THC(80-84):$6227.47 ($6792.80),

THC(70-79):$5713.47 ($6232.14),

THC(60-69):$5875.26 ($6408.62),

THC(40-59):$5817.58 ($6345.70),

THC(<40):$5249.12 ($5725.64),

PC(96-100):$449.86 ($490.70), PC(90-95):$439.74 ($479.66),

PC(85-89):$458.83 ($500.48),

PC(80-84):$423.15 ($461.56),

PC(70-79):$356.74 ($389.13),

PC(60-69):$371.30 ($405.01),

PC(40-59):$279.21 ($304.56),

PC(<40):$133.92 ($146.08),

MC(96-100):$3559.25 ($3882.36),

MC(90-95):$3666.81 ($3999.69),

MC(85-89):$3664 ($3996.62), MC(80-84):$3586.58 ($3912.17), MC(70-79):$3520.64 ($3840.25),

MC(60-69):$3551.99 ($3874.44), MC(40-59):$3663.65 ($3996.24),

MC(<40):$3499.95 ($3817.68)
Becker et al\textsuperscript{14} (2007, US) examined treatment outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries. The study was a retrospective cohort study with a follow-up of 2 years. The sample size was 10,330, with samples categorized as follows: >75% (6,609), 50-74% (1,276), 25-49% (1,940), <25% (505). The measure was the prescription refill rate, classified into maximal adherence (75-100%), moderate adherence (50-74.9%), minimal adherence (25-49.9%), and negligible adherence (<25%). The primary outcome was total costs, assessed using pharmacy claims data. The study found that as adherence decreased, costs increased significantly.

Eaddy et al\textsuperscript{15} (2005, US) evaluated the effect of partial compliance of patients with prescribed oral atypical and conventional antipsychotic agents and the corresponding impact on resource utilization. The study was a retrospective database analysis with a follow-up of 1 year. The sample size was 7,864, categorized as follows: <80% (2,655), 80-125% (5,065), >125% (1,44). The measure was continuous multiple interval medications available, with patients classified as partially compliant (<80%), compliant (80-125%), or overly compliant (>125%). The primary outcome was inpatient costs, outpatient costs, pharmacy costs, medical costs, physician office visit costs, other costs, and other costs. The study found that nonadherence led to increased costs and resource utilization.

Gilmer et al\textsuperscript{16} (2004) evaluated the relationship between medication adherence and total costs. The study was a retrospective database analysis. The measure was cumulative total costs, with costs classified as outpatient or inpatient. The primary outcome was the relationship between adherence and total costs. The study found a positive correlation between adherence and total costs.
adherence to treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.

**Follow Up:** 1 year
**Sample Size:** 1619
(<49%: 388, 50-79%: 259, 80-100%: 664, >110%: 308)

possession ratio

**Classification:**
- <49% = nonadherent
- 50-79% = partially adherent
- 80-100% = adherent
- >110% = excess medication fillers

Method of Assessment:
pharmacy claims data

costs

Pharmacy costs
Hospitalization costs

**Currency Year:** USD, 1999

Cost of Nonadherence:
- TC: $8168 ($11261.74)
- OC: $3464 ($4776.04)
- PC: $1542 ($2126.05)
- HC: $3413 ($4705.72)

**Quality:** medium

Hong et al[17] 2011 UK
To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.

**Design:** Prospective observational study
**Follow Up:** 21 months
**Sample Size:** 1341 (A: 1024, NA: 317)

**Measure:** assessed by treating psychiatrist

**Classification:**
- adherent vs. nonadherent

Method of Assessment:
observational assessment

**Total costs**

Inpatient costs
Outpatient costs

Pharmacy costs

Hospitalization costs

**Type of Costs:** unadjusted

**Classification:** all cause and disease state specific

**Currency Year:** GBP, 2008

Cost of Nonadherence:
- PC: £55.43 ($94.47)
- Disease state specific:
  - TC: £5846.29 ($9964.10)
  - IC: £2740.57 ($4670.88)
  - OC: £1082.86 ($1845.57)
  - PC: £1630.29 ($2778.58)
  - HC: £337.14 ($574.60)

**Quality:** medium

Jiang et al[18] 2015 US
To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization by controlling potential

**Design:** Retrospective cohort study
**Follow Up:** 2 years
**Sample Size:** 32374
(A: 11642, NA: 20732)

**Measure:** PDC

**Classification:**
- (PDC≥80% = adherent, PDC<80% = nonadherent)

Method of Assessment:
observational assessment

**Total costs**

Pharmacy costs
Medical services costs

**Currency Year:** USD, 2011

Cost of Nonadherence:
- Disease state specific:
  - TC: $14141 ($14517.37)
  - MSC: $10170 ($10440.68)

**Quality:** low

Classification: cost description
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Classification</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joe et al [19]</td>
<td>2016</td>
<td>South Korea</td>
<td>To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>7848 (A:2774, NA:2774, P:1956, NP:1956)</td>
<td>Percentage of days of psychiatric prescription (PDP)</td>
<td>PDP≥80% = adherent, PDP&lt;80% = nonadherent; persistent = continued medication without interruption ≥ 56 day, non-persistent = at least one medication interruption &gt; 56 days</td>
<td>Total costs</td>
<td>Type of Costs: adjusted</td>
<td>Classification: all cause and disease state specific</td>
<td>Currency Year: USD, 2011</td>
<td>Cost of Nonadherence: TC:$4961 ($5271.40) Disease state specific: TC:$3061 ($3252.50)</td>
<td>medium</td>
<td>cost outcome description</td>
</tr>
</tbody>
</table>
### Offord et al [21]

#### 2013

**US**

To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilisation and costs.

**Design:** Retrospective cohort study  
**Follow Up:** 1 year  
**Sample Size:** 1462 (A:589, NA:873)

**Assessment:**  
**Survey**  
**Measure:** time to discontinuation  
**Classification:** adherent vs. nonadherent

**Method of Assessment:** pharmacy claims data

**Total costs**  
**Outpatient costs**  
**Pharmacy costs**  
**Hospitalization costs**

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2008

**Cost of Nonadherence:** all cause:  
**TC:** $15400 ($17132.34)  
**OC:** $5773 ($6422.40)  
**PC:** $3777 ($4201.87)  
**HC:** $5850 ($6508.06)

**Disease state specific:**  
**TC:** $5358 ($5960.72)  
**OC:** $858 ($954.52)  
**PC:** $1549 ($1723.25)  
**HC:** $2952 ($3284.07)

**Quality:** medium

### Offord et al [22]

#### 2013

**US**

To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.

**Design:** Retrospective cohort study  
**Follow Up:** 1 year  
**Sample Size:** 354 (A:126, NA:228)

**Assessment:**  
**MPR**  
**Classification:** MPR ≥ 70= high adherence, MPR < 70 = low adherence

**Method of Assessment:** pharmacy claims data

**Inpatient costs**  
**Pharmacy costs**

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2008

**Cost of Nonadherence:** all cause:  
**IC:** $9053 ($10071.37)  
**PC:** $4267 ($4746.99)

**Disease state specific:**  
**IC:** $2468 ($2745.62)  
**PC:** $1085 ($1207.05)

**Quality:** low

### Robinson et al [23]

#### 2006

**US**

To determine if the type of antidepressant drug is related to adherence and assess the 6 month healthcare costs among newly diagnosed

**Design:** Retrospective claims analysis  
**Follow Up:** 6 months  
**Sample Size:** 60386 (A:11526, NA:8860)

**Assessment:**  
**Antidepressant medication management measures**  
**Classification:** meeting less than  
**ED visit costs**  
**Pharmacy costs**

**Type of Costs:** unadjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2004

**Cost of Nonadherence:** all cause:  
**TC:** $12658 ($15678.21)  
**IC:** $3006 ($3723.24)
patients.

<3 medication management measures = nonadherent
Method of Assessment: pharmacy claims data, Medicaid data, observational assessment

<table>
<thead>
<tr>
<th>Costs</th>
<th>Type of Costs</th>
<th>Disease state specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC: $6118 ($7577.76), EDC: $334 ($413.69), PC: $3200 ($3963.52), POC: $178 ($220.47)</td>
<td>unadjusted</td>
<td></td>
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<tr>
<td>Disease state specific:</td>
<td></td>
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<tr>
<td>TC: $2028 ($2511.88), IC: $102 ($126.34), OC: $734 ($909.13), EDC: $18 ($22.29), PC: $1174 ($1454.12), POC: $120 ($148.63)</td>
<td>all cause and disease state specific</td>
<td></td>
</tr>
</tbody>
</table>

**Svarstad et al[24]**
2001 US
To examine the relationship of medication non-adherence to hospital use and costs among severely mentally ill clients.

Design: Retrospective database analysis Follow Up: 1 year Sample Size: 619 (A:413, NA:206)
Measure: quarter pharmacy claims Classification: one or more quarters without a claim = nonadherent Method of Assessment: pharmacy claims data, previous study data
Hospitalization costs
Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 1990
Cost of Nonadherence: all cause: HC: $3992 ($6593.06), Disease state specific: Schizophrenia/schizoaffective disorder: HC: $3421 ($5650.01), Bipolar disorder: HC: $9701 ($16021.85), Other severe mental illness: HCD: $3024 ($4994.34)

**White et al[25]**
2003 US
To evaluate the economic impact of antidepressant treatment adherence among patients treated for depression

Design: Retrospective database analysis Follow Up: 6 months Sample Size: 14190 (A:5638, NA:8552)
Measure: MPR Classification: MPR ≥70% = adherent, MPR <70% = nonadherent Method of Assessment: pharmacy claims
Total costs Pharmacy costs Medical costs
Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 1999
Cost of Nonadherence: TC: $11815 ($16290.09), PC: $1123 ($1548.35), MC: $10692 ($14741.74)
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Follow-Up</th>
<th>Sample Size</th>
<th>MPR Classification</th>
<th>Measure</th>
<th>Total Costs</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>An et al[26]</td>
<td>2014</td>
<td>Korea</td>
<td>Prospective cohort study</td>
<td>3 years</td>
<td>608 (A:472, NA:136)</td>
<td>MPR ≥ 90% = adherent, MPR &lt; 90% = nonadherent</td>
<td>MPR</td>
<td>Total costs</td>
<td>Unadjusted</td>
<td>Classification: disease state specific</td>
<td>Medium</td>
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<td>Hospitalization costs</td>
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<td>Cost of Nonadherence: TC: $1657.11 ($1884.14)</td>
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<td>Outpatient costs</td>
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<td>OC: $1413.99 ($1608.20),</td>
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<td>Inpatient costs</td>
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<td>HC: $243.11 ($276.12)</td>
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<td>Pharmacy costs</td>
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<td></td>
<td>Egede et al[27]</td>
<td>2012</td>
<td>US</td>
<td>Retrospective cohort study</td>
<td>5 years</td>
<td>740195 (A:427390, NA:312805)</td>
<td>MPR ≥ 80% = adherent, MPR &lt; 80% = nonadherent</td>
<td>MPR</td>
<td>Total costs</td>
<td>Unadjusted</td>
<td>Classification: disease state specific</td>
<td>High</td>
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<td>Hospitalization costs</td>
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<td>Cost of Nonadherence: IC: $14515.24 ($17886.40)</td>
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<td>Outpatient costs</td>
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<td>OC: $3599.27 ($4434.16),</td>
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<td>Inpatient costs</td>
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<td>PC: $1073.12 ($1322.42)</td>
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<td>Pharmacy costs</td>
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<tr>
<td></td>
<td>Gentil et al[28]</td>
<td>2015</td>
<td>Canada</td>
<td>Retrospective, observational cohort analysis</td>
<td>1 year</td>
<td>301 (A:224, NA:77)</td>
<td>MPR ≥ 80% = adherent, MPR &lt; 80% = nonadherent</td>
<td>MPR</td>
<td>Total costs</td>
<td>Adjusted and unadjusted</td>
<td>Classification: all cause and disease state specific</td>
<td>Medium</td>
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<td>Hospitalization costs</td>
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<td>Cost of Nonadherence: Adjusted all cause: TC: $11124 ($9818.67),</td>
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<td>Outpatient costs</td>
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<td>IC: $7419 ($6548.43)</td>
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<td>Inpatient costs</td>
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<td>OC: $2687 ($2371.70)</td>
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<td></td>
<td>Physician office visit costs</td>
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<tr>
<td>Hagen et al[29]</td>
<td>To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/short term disability costs</td>
<td>Design: Retrospective, observational cohort analysis</td>
<td>Measure: PDC  Classification: PDC≥80% = compliant, PDC&lt;80% = noncompliant</td>
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<tr>
<td>2014 US</td>
<td>Follow Up: 1 year</td>
<td>Classification: all cause and disease state specific</td>
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<tr>
<td>Sample Size: 4978 (A:2820, NA:2158)</td>
<td>Type of Costs: adjusted and unadjusted</td>
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<td>Quality: medium</td>
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</tbody>
</table>

### Healthcare costs
- **PC:** $504 ($444.86), POC: $513 ($452.80)
- **Adjusted disease state specific:**
  - **TC:** $4477 ($3951.65), IC: $2836 ($2503.21)
  - **OC:** $1518 ($1339.87), PC: $-444 ($-391.90), POC: $568 ($517.24)
- **Unadjusted all cause:**
  - **TC:** $14979 ($13221.30), IC: $6351 ($5605.75)
  - **OC:** $4058 ($3581.82), PC: $3503 ($3091.94), POC: $1066 ($940.91)
  - **Unadjusted disease state specific:**
    - **TC:** $9008 ($7950.97), IC: $2854 ($2519.10)
    - **OC:** $2654 ($2342.57), PC: $2498 ($2204.87), POC: $1002 ($884.42)

### Pharmacy costs
- **Type of Costs:** adjusted and unadjusted
- **Classification:** all cause and disease state specific
- **Currency Year:** USD, 2003
- **Cost of Nonadherence:** Adjusted all cause:
  - **PC:** $1668 ($2065.99)
  - **Adjusted disease state specific:**
    - **HC:** $7642 ($9465.39), PC: $614 ($760.50), MC: $5974 ($7399.40), STDC: $1840 ($2279.03)
  - **Unadjusted all cause:**
    - **PC:** $1727 ($2139.06)
    - **POC:** $1066 ($940.91)
To compare all cause total health care costs and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.

**Design:** Retrospective, cohort study  
**Follow Up:** 2 years  
**Sample Size:** 108592 (A:63830, NA:44762)

**Measure:** MPR  
**Classification:** MPR≥80% = adherent, MPR<80% = nonadherent

**Assessment:** pharmacy claims data

<table>
<thead>
<tr>
<th>Total Healthcare costs</th>
<th>Unadjusted disease state specific: HC:$6919 ($8569.88), PC:$785 ($972.30), MC:$5192 ($6430.82), STDC:$1717 ($2126.68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient costs</td>
<td>Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific</td>
</tr>
<tr>
<td>Outpatient costs</td>
<td><strong>Currency Year:</strong> USD, 2005</td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td><strong>Cost of Nonadherence</strong>: Adjusted all cause: THC:$13258 ($15911.01)</td>
</tr>
</tbody>
</table>

**Quality:** medium

**Classification:** cost description

---

To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.

**Design:** Retrospective, cohort study  
**Follow Up:** 3 years  
**Sample Size:** 40082 (A:11800, NA:28282)

**Measure:** MPR  
**Classification:** MPR≥80% = adherent, MPR<80% = nonadherent

**Assessment:** pharmacy claims data

**Total costs** Hospitalization costs

**Cost of Nonadherence:**

- TC:₩765453 ($1142.31), HC:₩397549 ($593.28)

**Quality:** medium

**Classification:** cost description

---

How often do previously non-

**Design:** Retrospective, observational claims

**Measure:** MPR  
**Classification:** MPR≥80% = adherent, MPR<80% = nonadherent

**Assessment:** pharmacy claims data

**Total costs** ED costs

**Type of Costs:** adjusted  
**Classification:** disease state specific

**Quality:** high

**Classification:** cost description
adherent patients become adherent and vice versa? Are changes in adherence associated with increased or decreased hospitalizations or emergency department visits? Are there certain subgroups of populations that seem to benefit more than others when they adhere to their medication? What are the financial implications of changes in adherence for the nation at large and for Medicare?

**MPR**
- \( \geq 80\% = \) adherent,
- \(< 80\% = \) nonadherent

**Method of Assessment:** pharmacy claims data

**Follow Up:** unclear

**Sample Size:** 135639 (A:99976, NA:36553)

<table>
<thead>
<tr>
<th>MPR Classification</th>
<th>Hospitalization costs</th>
<th>Total costs</th>
<th>Non-pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td></td>
<td>Pharmacy costs</td>
<td></td>
</tr>
<tr>
<td>≥95%</td>
<td>TC: $46800000000</td>
<td>TC(≥95): $4835</td>
<td>$6518.17</td>
</tr>
<tr>
<td></td>
<td>EDC: $73500000000</td>
<td>TC(75-95): $5314</td>
<td>$7163.92</td>
</tr>
<tr>
<td></td>
<td>HC: $39500000000</td>
<td>PC&lt;75%: $762</td>
<td>$1027.27</td>
</tr>
</tbody>
</table>

**Follow Up:** 1 year

**Sample Size:** 67029 (>95:20170, 75-95: 14074, <75:16713)

**Design:** Retrospective, database analysis

**Measure:** MPR

**Classification:**
- MPR≥95%,
- MPR>75%<95%,
- MPR<75%

**Method of Assessment:** pharmacy claims data

**Cost of Nonadherence***:
- TC: $46800000000 (5006563305.49),
- EDC: $73500000000 (786287185.80),
- HC: $39500000000 (4225625012.11)

**Hospitalization costs**

**Type of Costs:** adjusted and unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2000

**Cost of Nonadherence:** adjusted:
- TC(≥95): $4835 ($6518.17),
- TC(75-95): $5314 ($7163.92),
- TC(<75): $5706 ($7692.38),
- PC(≥95): $1429 ($1926.47),
- PC(75-95): $1157 ($1559.78),
- PC(<75): $762 ($1027.27),
- NPC(≥95): $3406 ($4591.70),

**Quality:** low

**Classification:** cost analysis

**Outcome description**

*White et al [33] 2004

US To assess the relationship between diabetic medication adherence, total healthcare costs and utilisation with patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease.
Wu et al[34] 2009 US

To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

Design: Retrospective, cohort study
Follow Up: 1 year
Sample Size: 2354 (A:830, NA:1524)

Measure: MPR
Classification:
MPR≥80% = high compliance,
MPR<80% = low compliance

Subgroup Analysis:
commercial and Medicare supplemental

Method of Assessment:
pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2006
Cost of Nonadherence: adjusted all cause:

THC(com):$32407 ($37732.29),
THC(med):$24622 ($28668.02),
IC(com):$ 12851($14692.74),
IC(med):$ 6754 ($7863.85),
OC(com):$11888 ($13841.50),
OC(med):$10598 ($12339.52),
PC(com):$7667 ($8926.88),
PC(med):$7270 ($8464.65)

Adjusted disease state specific:
Diabetes:
THC(com):$10024 ($11671.20),
THC(med):$5015 ($5839.09),
IC(com):$ 2232 ($2598.77),
IC(med):$2606 ($3034.23),
OC(com):$1989 ($2315.84),

NPC(≥95):$4157 ($5604.14),
NPC(<75):$4944 ($6665.11)

Unadjusted:
TC(≥95):$4809 ($6483.12),
TC(75-95):$5333 ($7189.53),
TC(<75):$5605 ($7556.22),
PC(≥95):$1402 ($1890.07),
PC(75-95):$1153 ($1554.38),
PC(<75):$766 ($1032.66),

NPC(≥95):$3407 ($4593.05),
NPC(<75):$4839 ($6523.56)

Wu et al[34] 2009 US
Osteoporosis
Briesacher et al[35] 2007 US
To assess rates of osteoporotic fractures and health care utilization as a function of bisphosphonate compliance in usual clinical practice.

**Osteoporosis**

**Design:** Retrospective, cohort study  
**Follow Up:** 3 years  
**Sample Size:** 17988 (not specified)

**Measure:** MPR  
**Classification:** 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent

**Method of Assessment:** pharmacy claims data

**Type of Costs:** adjusted and unadjusted  
**Currency Year:** USD, 2004

**Cost of Nonadherence:**
- **TC(80-100):** $859 (-$1063.96),  
- **TC(60-79):** $474 (-$587.10),  
- **TC(40-59):** $366 (-$453.33),  
- **TC(20-39):** $151 ($187.03),  
- **IC(80-100):** $3233 (-$4004.40),  
- **IC(60-79):** $856 (-$1060.24),  
- **IC(40-59):** $6221 (-$7705.34),  
- **IC(20-39):** $585 (-$724.58),  
- **OC(80-100):** $445 (-$551.18),  
- **OC(60-79):** $538 (-$666.37),  
- **OC(40-59):** $236 (-$292.31),  
- **OC(20-39):** $60 ($74.32),  
- **PC(80-100):** $997 ($1234.89),  
- **PC(60-79):** $923 ($1143.23),  
- **PC(40-59):** $402 ($497.92),  
- **PC(20-39):** $160 ($198.18)

**Quality:** medium  
**Classification:** cost description
To determine healthcare outcomes associated with compliance and noncompliance to bisphosphonate therapy in women diagnosed with osteoporosis.

**Design:** Retrospective claims study

**Follow Up:** 2 years

**Sample Size:** 27905 (A:11368, NA:16537)

**Measure:** MPR

**Classification:** (≥70% = compliant, <70% = noncompliant)

**Method of Assessment:** pharmacy claims data

**Total costs**

- **Inpatient costs**
- **Outpatient costs**
- **ED costs**
- **Pharmacy costs**
- **Physician office visit costs**

**Type of Costs:** unadjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2012

**Cost of Nonadherence:** all cause:
- **TC:** $7237 ($7550.72),
- **IC:** $1986 ($2072.09),
- **OC:** $2057 ($2146.17),
- **EDC:** $258 ($269.18),
- **PC:** $2197 ($2292.24),
- **POC:** $738 ($769.99)

**Disease state specific:**
- **TC:** $674 ($703.22),
- **IC:** $334 ($348.48),
- **OC:** $77 ($80.34),
- **EDC:** $5 ($5.22)

**Quality:** medium

**Classification:** cost description

---

Unadjusted:
- **TC (80-100):** -$1273 (-$1576.74),
- **TC (60-79):** -$294 (-$364.15),
- **TC (40-59):** -$573 (-$709.72),
- **TC (20-39):** $101 ($125.10),
- **IC (80-100):** -$883 (-$1093.68),
- **IC (60-79):** -$384 (-$475.62),
- **IC (40-59):** -$597 (-$739.44),
- **IC (20-39):** -$93 (-$115.19),
- **OC (80-100):** -$774 (-$958.68),
- **OC (60-79):** -$193 (-$239.05),
- **OC (40-59):** -$145 (-$179.60),
- **OC (20-39):** $148 ($183.31),
- **PC (80-100):** $384 ($475.62),
- **PC (60-79):** $284 ($351.76),
- **PC (40-59):** $170 ($210.56),
- **PC (20-39):** $48 ($59.45)
Halpern et al[37] 2011 US
To examine the associations of adherence to osteoporosis therapies with occurrence of closed fracture, all cause medical costs and all cause hospitalizations.

Design: Retrospective analysis
Follow Up: 540 days
Sample Size: 21655
(≥80%:8759, ≥50<80%:5237, <50%:7659)

Measure: MPR
Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence

Method of Assessment: pharmacy claims data

Medical costs
Type of Costs: unadjusted
Classification: all cause
Currency Year: USD, 2006
Cost of Nonadherence:
MC(≥80):$4295 ($5000.78),
MC(50-80):$4697 ($5468.84),
MC(<50):$5596 ($6515.56)

Medicare:
MC(≥80):$4590 ($5344.25),
MC(50-80):$5536 ($6445.71),
MC(<50):$5801 ($6754.25)

Quality: medium
Classification: cost outcome description

Hazel-Fernandez et al[38] 2013 US
To evaluate the healthcare utilisation patterns of medicare part D beneficiaries newly initiating teriparatide and to assess the association of medication adherence and persistence with bone fracture.

Design: Retrospective cohort study
Follow Up: 12 months
Sample Size: 761
(≥80%:163, ≥50<80%:57, <50%:541)

Measure: PDC
Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence

Method of Assessment: pharmacy claims data

Total healthcare costs
Type of Costs: unadjusted
Classification: disease state specific and fracture related
Currency Year: USD, 2010
Cost of Nonadherence:
Disease state specific:
THC(≥80):$21033 ($22942.39),
THC(50-80):$25574 ($27895.62),
THC(<50):$15528 ($16937.64),
IC(≥80):$2198 ($2397.54),
IC(50-80):$8448 ($9214.91),
IC(<50):$4897 ($5341.55),
OC(≥80):$5151 ($5618.61),
OC(50-80):$6439 ($7023.54),
OC(<50):$5806 ($6333.07),
EDC(≥80):$211 ($230.15),
EDC(50-80):$330 ($359.96),
EDC(<50):$465 ($507.21),
PC(≥80):$13472 ($14695),
PC(<50):$1374 ($1491.54),

Quality: medium
Classification: cost outcome description
For peer review only

Huybrechts et al[39] 2006 US
To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.

Design: Retrospective cohort study
Follow Up: 5 years
Sample Size: 38120 (A:9530, NA:28590)

Measure: MPR
Classification: (≥80% = compliant, <50% = noncompliant)
Method of Assessment: pharmacy claims data

Total costs
Medical costs
Institutional costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2000
Cost of Nonadherence:
TC:$10810 ($11791.34),
PC(≥80):$10358 ($11298.31),
PC(<50):$4361 ($4756.89)
Fracture related:
THC(≥80):$12670 ($13820.19),
THC(50-80):$9292 ($10135.53),
THC(<50):$4419 ($4820.16),
IC(≥80):$366 ($399.23),
IC(50-80):$830 ($905.35),
IC(<50):$1325 ($1445.28),
OC(≥80):$1048 ($1143.14),
OC(50-80):$955 ($1041.70),
OC(<50):$767 ($836.63),
EDC(≥80):$6 ($6.54),
EDC(50-80):$9 ($9.82),
EDC(<50):$44 ($47.99),
PC(≥80):$10358 ($11298.31),
PC(50-80):$9292 ($10135.53),
PC(<50):$4419 ($4820.16)

Quality: low
Classification: cost description

Kjellberg et al[40] 2016 Denmark
To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 38234 (A:26806, NA:11428)

Measure: MPR
Classification: (≥70% = compliant, <70% = noncompliant)
Method of Assessment: pharmacy claims data

Total costs
Medical costs
Institutional costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: Euro, 2011
Cost of Nonadherence: all cause:
TC:€4933 ($6209.58),
PC(≥80):€10810 ($11791.34),
PC(<50):€4361 ($4756.89)
Fracture related:
THC(≥80):€12670 ($13820.19),
THC(50-80):€9292 ($10135.53),
THC(<50):€4419 ($4820.16),
IC(≥80):€366 ($399.23),
IC(50-80):€830 ($905.35),
IC(<50):€1325 ($1445.28),
OC(≥80):€1048 ($1143.14),
OC(50-80):€955 ($1041.70),
OC(<50):€767 ($836.63),
EDC(≥80):€6 ($6.54),
EDC(50-80):€9 ($9.82),
EDC(<50):€44 ($47.99),
PC(≥80):€10810 ($11791.34),
PC(<50):€4419 ($4820.16)

Quality: high
Classification: cost outcome description
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Modi et al [41] 2015 US</td>
<td>Retrospective cohort study</td>
<td>MPR</td>
<td>≥80% = compliant, &lt;80% = noncompliant</td>
<td>unadjusted</td>
<td>medium</td>
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<tr>
<td>Olsen et al [42] 2013 Denmark</td>
<td>Retrospective observational study</td>
<td>MPR</td>
<td>≥80% = optimal compliance, &gt;50&lt;80% = suboptimal compliance, &lt;50% = low compliance</td>
<td>fracture site specific</td>
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<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
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<tr>
<td>Sunyecz et al [43] 2008 US</td>
<td>To examine the relationship between persistence and compliance with bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naïve users.</td>
<td>Retrospective observational study</td>
<td>3 years</td>
<td>32944 (A:12186, NA:20758)</td>
<td>MPR</td>
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<tr>
<td>Zhao et al [44] 2014 US</td>
<td>To examine the association between teriparatide adherence and healthcare utilisation and costs</td>
<td>Retrospective cohort study</td>
<td>36 months</td>
<td>824 (≥80:362, 50-80%:219, &lt;50%:243)</td>
<td>PDC</td>
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<tr>
<td>Method of Assessment</td>
<td>Total healthcare costs</td>
<td>Inpatient costs</td>
<td>Outpatient costs</td>
<td>Pharmacy costs</td>
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<tr>
<td>THC(≥80)</td>
<td>$34428 ($37553.4)</td>
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<td>THC(50-80)</td>
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<td>THC(&lt;50)</td>
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<td>IC(≥80)</td>
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<td>IC(50-80)</td>
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<td>IC(&lt;50)</td>
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<td>OC(≥80)</td>
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<tr>
<td>OC(50-80)</td>
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<td>OC(&lt;50)</td>
<td>$13044 ($14228.16)</td>
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<tr>
<td>PC(≥80)</td>
<td>$18864 ($20576.52)</td>
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<tr>
<td>PC(50-80)</td>
<td>$13116 ($14306.64)</td>
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<tr>
<td>PC(&lt;50)</td>
<td>$7452 ($8128.44)</td>
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</tr>
</tbody>
</table>

Unadjusted:
| THC(≥80)            | $37464 ($40865.04)     |                 |                 |               |
| THC(50-80)          | $35076 ($38260.20)     |                 |                 |               |
| THC(<50)            | $29484 ($32160.60)     |                 |                 |               |
| IC(≥80)             | $7092 ($7735.80)       |                 |                 |               |
| IC(50-80)           | $11100 ($12107.64)     |                 |                 |               |
| IC(<50)             | $10632 ($11597.16)     |                 |                 |               |
| OC(≥80)             | $9900 ($10798.68)      |                 |                 |               |
| OC(50-80)           | $11352 ($12382.56)     |                 |                 |               |
| OC(<50)             | $11988 ($13076.28)     |                 |                 |               |
| PC(≥80)             | $20484 ($22343.52)     |                 |                 |               |
| PC(50-80)           | $12624 ($13770)        |                 |                 |               |
| PC(<50)             | $6864 ($7487.16)       |                 |                 |               |

Zhao et al [45] 2013 US
To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebrop

Design: Retrospective observational cohort study
Follow Up: 36 months
Sample Size: 1568
(≥80: 783, 50-80%: 382, <50%: 403)

Measure: PDC
Classification: (≥80% = high, 50-80% = medium, <50% = low)

Method of Assessment: pharmacy claims data

Cost of Nonadherence:
- Adjusted:
  - THC(≥80): $40212 ($43862.52),
  - THC(50-80): $40512 ($44189.76),
  - THC(<50): $40128 ($43770.84),

Quality: medium
Classification: cost description
Currency Year: USD, 2010
Type of Costs: adjusted and unadjusted
classification: disease state specific
To assess the association between adherence with fluticasone propionate/salmeterol combination product in a single inhaler and asthma care utilization and costs in asthma.

**Design:** Retrospective longitudinal cohort study

**Follow Up:** 24 months

**Sample Size:** 12907

$\geq 75$: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652

**Measure:** MPR

**Classification:**

$\geq 75$, 50-75%, 25-50%, <25%

**Method of Assessment:** pharmacy claims data

**Total costs**

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2003

**Cost of Nonadherence:**

TC($\geq 75$): $1564 ($1990.27),
TC(50-75): $1128 ($1435.44),
TC(25-50): $900 ($1145.30),
TC(<25): $632 ($804.25),
OC($\geq 75$): $14580 ($15903.60),
OC(50-75): $12108 ($13207.20),
OC(25-50): $900 ($1145.30),
OC(<25): $632 ($804.25),
PC($\geq 75$): $20568 ($22435.20),
PC(50-75): $12444 ($13573.68),
PC(25-50): $8700 ($9489.84),
PC(<25): $8700 ($9489.84)

**Data**

IC($\geq 80$): $8136 ($8874.60),
IC(50-80): $12060 ($13154.76),
IC(<50): $15444 ($43404.36),
OC($\geq 80$): $12924 ($14097.24),
OC(50-80): $14928 ($16283.16),
OC(<50): $17568 ($19162.80),
PC($\geq 80$): $19392 ($21152.40),
PC(50-80): $13908 ($15170.52),
PC(<50): $8700 ($9489.84)

Unadjusted:

THC($\geq 80$): $42768 ($46650.48),
THC(50-80): $36780 ($40118.88),
THC(<50): $39792 ($43404.36),
IC($\geq 80$): $7620 ($8311.80),
IC(50-80): $12228 ($13338.12),
IC(<50): $15768 ($17199.48),
OC($\geq 80$): $14580 ($15903.60),
OC(50-80): $12108 ($13207.20),
OC(<50): $15324 ($16715.16),
PC($\geq 80$): $20568 ($22435.20),
PC(50-80): $12444 ($13573.68),
PC(<50): $8700 ($9489.84)
patients in typical US clinical practice

To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and received palivizumab in accordance with the dosing schedule recommended by the American Academy of Paediatrics in 2006 versus those who did not.

**Design:** Retrospective claims analysis
**Follow Up:** 7 months
**Sample Size:** 245 (A:73, NA:172)

**Measure:** 37 day gap in claims
**Classification:** (>37 day gap in claims = noncompliant)

**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted
disease state specific

**Currency Year:** USD, 2007

**Cost of Nonadherence:**
TC:$19093.46 ($21656.12),
PC:$7647.40 ($8673.81),
SC:* $11604.03 ($13161.45)

---

Examine the association of medication adherence with workplace productivity and health related quality of life in asthma patients.

**Design:** quantitative analysis
**Follow Up:**
**Sample Size:** 385 (high:150, medium:73, low: 162)

**Measure:** Morisky scale
**Classification:** (0= high adherence, 1-2 = medium adherence, >2 = low adherence)

**Method of Assessment:**

**Type of Costs:** unadjusted
disease state specific

**Currency Year:** USD, 2002

**Cost of Nonadherence**

**TPC(0):** $1210.90 ($1571.73),
**TPC(1-2):** $1428.50 ($1854.17),
**TPC(>2):** $1073.10 ($1392.87),
**AbC(0):** $633.70 ($822.53),
**AbC(1-2):** $608.90 ($790.34),
**AbC(>2):** $547.40 ($707.87),

**Quality:** medium
cost outcome description
To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).

**Design:** multicentre, retrospective, observational study  
**Follow Up:** 18 months  
**Sample Size:** 1365 (A:246, NA:1119)

**Measure:** GOLD 2007 Guidelines  
**Classification:** (adherent, nonadherent)  
**Method of Assessment:** GOLD guidelines

**Type of Costs:** unadjusted  
**Classification:** disease state specific  
**Currency Year:** EUR, 2009

Cost of Nonadherence:
- EDC:€40.83 ($57.91)  
- PC:€771.50 ($1094.27)  
- POC:€106.29 ($150.76)  
- HC:€101.61 ($144.12)  
- PCC:€123.84 ($175.65)  
- IntC:€321.44 ($455.92)  
- MTC:€36.66 ($51.99)  
- RC:€24.24 ($34.38)  
- LC:€17.35 ($24.61)

**Quality:** medium

Quittner et al[50]  
2014  
US

To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.

**Design:** retrospective, cohort study  
**Follow Up:** 2 years  
**Sample Size:** 3287  
(≥80%: 663, 50-80%: 949, <50%: 1675)

**Measure:** MPR  
**Classification:** (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence)  
**Method of Assessment:** pharmacy claims

**Type of Costs:** unadjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 2011

Cost of Nonadherence:
- THC(≥80):$35749.50 ($38244.05)  
- THC(50-80):$45031.50 ($48173.73)  
- THC(<50):$50284.50 ($53793.28)

**Quality:** medium
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Measure</th>
<th>Type of Costs</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disease</strong> Carter et al [51] 2011 US</td>
<td>Retrospective, observational cohort claims analysis</td>
<td>Hospitalization costs</td>
<td>Unadjusted</td>
<td>Medium</td>
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<tr>
<td>Follow Up: 12 months</td>
<td>Sample Size: 638 (A:466, NA:172)</td>
<td>Classification: (7-9 infusions = adherent, &lt;7 infusions = nonadherent)</td>
<td>Disease state specific</td>
<td>USD 2007</td>
</tr>
<tr>
<td>*THC (≥80): $23764 ($25422.22), THC (50-80): $33132.50 ($35444.44), THC (&lt;50): $33894 ($36259.07)*</td>
<td></td>
<td></td>
<td>Cost of Nonadherence: HC: $37783 ($42854.12)</td>
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<tr>
<td>Gosselin et al [52] 2009 US</td>
<td>Retrospective cohort study</td>
<td>Total costs Inpatient costs Outpatient costs Pharmacy costs Medical costs</td>
<td>Adjusted</td>
<td>Medium</td>
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<tr>
<td>Follow Up:</td>
<td>Sample Size: 41837 (A:28321, NA:13516)</td>
<td>Classification: (≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Disease state specific</td>
<td>USD 2003</td>
</tr>
<tr>
<td>Design: retrospective, observational cohort claims analysis</td>
<td>Measure: MPR</td>
<td>Type of Costs:</td>
<td>Cost of Nonadherence: TC: $9497 ($12085.43), IC: $2116 ($2692.72), OC: $5458 ($6945.59), PC: $1922 ($2445.85), MC: $7575 ($9639.58)</td>
<td>Medium</td>
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<tr>
<td>Method of Assessment: pharmacy claims data</td>
<td>Type of Costs:</td>
<td>Classification:</td>
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<td>Cost description</td>
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<tr>
<td>Kane et al [53] 2009 US</td>
<td>Retrospective cohort analysis</td>
<td>Hospitalization costs</td>
<td>Unadjusted</td>
<td>Medium</td>
</tr>
<tr>
<td>Follow Up: 12 months</td>
<td>Sample Size: 571 (A:375, NA:196)</td>
<td>Classification: (≥8 infusions = adherent, &lt;7 infusions = nonadherent)</td>
<td>All cause and disease state specific</td>
<td>USD 2004</td>
</tr>
<tr>
<td>Design: retrospective, observational cohort claims analysis</td>
<td>Measure: number of infusions in 12 month period</td>
<td>Type of Costs:</td>
<td>Cost of Nonadherence: All cause: OC: $6679 ($8272.62),</td>
<td>Medium</td>
</tr>
<tr>
<td>Method of Assessment: pharmacy claims data</td>
<td>Classification: (7-9 infusions = adherent, &lt;7 infusions = nonadherent)</td>
<td>Classification:</td>
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<td>Cost description</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
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<tr>
<td>Mitra et al[54]</td>
<td>2012</td>
<td>US</td>
<td>To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.</td>
<td>Retrospective, observational cohort study</td>
</tr>
<tr>
<td>Wan et al[55]</td>
<td>2014</td>
<td>US</td>
<td>To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.</td>
<td>Retrospective cohort analysis</td>
</tr>
</tbody>
</table>
Epilepsy

Davis et al[56]
2008 US
To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 10892 (A:6644, NA:4248)

Measure: MPR
Classification:
(≥80% = adherent, <80% = nonadherent)
Method of Assessment: pharmacy claims data

Total costs
Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence:
TC:$1466 ($1865.56),
IC:$1799 ($2289.32),
EDC:$260 ($330.86),
PC:-$71 (-$90.35),
OtPC:-$358 (-$455.57)

Quality: medium
Classification: cost outcome description

Ettinger et al[57]
2009 US
To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 1278 (A:758, NA:520)

Measure: MPR
Classification:
(≥80% = adherent, <80% = nonadherent)
Method of Assessment: pharmacy claims data

Total costs
Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003
Cost of Nonadherence:
TC:$17817 ($22673.06),
IC:$2714 ($3453.71),
EDC:$526 ($669.36),
PC:$347 ($441.58),
POC:$3063 ($3897.83),
AC:$8344 ($10618.18),
OtPC:$2822 ($3591.14)

Quality: medium
Classification: cost outcome description

Faught et al[58]
To study the impact of

Design: retrospective
Measure: MPR
Total costs
Type of Costs: unadjusted
Quality: medium
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Measured</th>
<th>Measure</th>
<th>Total Costs</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>US</td>
<td>Observational</td>
<td>4.65 years</td>
<td>33,658</td>
<td>(≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Pharmacy claims data</td>
<td>Antiretroviral taking behaviour</td>
<td>85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent</td>
<td>Total costs</td>
<td>Unadjusted</td>
<td>THC:$14,417.64 ($18,713.91), IC:$6,682.28 ($6,873.51), OC:$2,172.40 ($2,819.75), EDC:$405.96 ($526.93), PC:$822.40 ($1,067.46), OtPC:$4,334.60 ($5,626.26)</td>
<td>Medium</td>
</tr>
<tr>
<td>2011</td>
<td>US</td>
<td>Retrospective</td>
<td>1 year</td>
<td>1,896</td>
<td>(85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent)</td>
<td>Pharmacy claims data</td>
<td>MPR</td>
<td>≥90% = adherent, &lt;90% = nonadherent</td>
<td>Total healthcare costs</td>
<td>Unadjusted</td>
<td>THC:$25,824 ($30,067.54), Low viral load: THC:$20,509.67 ($23,879.92)</td>
<td>Medium</td>
</tr>
<tr>
<td>2014</td>
<td>US</td>
<td>Retrospective</td>
<td>1 year</td>
<td>3,528</td>
<td>(≥90% = adherent, &lt;90% = nonadherent)</td>
<td>Pharmacy claims data</td>
<td>MPR</td>
<td>≥90% = adherent, &lt;90% = nonadherent</td>
<td>Total healthcare costs</td>
<td>Unadjusted</td>
<td>THC:$18,868 ($20,184.58), IC:$2,700 ($2,888.40), OC:$915 ($978.85), PC:$15,253 ($16,317.33)</td>
<td>Medium</td>
</tr>
</tbody>
</table>
associated with ≥90% adherence.

To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.

**Pruiit et al[61]**

2015

US

To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.

**Design:** retrospective cohort study

**Follow Up:** 2 years

**Sample Size:** 502 (A:56, NA:176)

**Measure:** MPR

**Classification:**

(≥90% = adherent, <90% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Total costs**

<table>
<thead>
<tr>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy costs</td>
<td>Other pharmacy costs</td>
</tr>
<tr>
<td>Behavioural health inpatient costs</td>
<td></td>
</tr>
</tbody>
</table>

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2009

**Cost of Nonadherence:**

HIV:

TC:$15360 ($16957.32), IC:$3864 ($4265.76), OC:$3948 ($4358.52), PC:$4956 ($5471.40), OtPC:$1764 ($1947.48), BHIC:$840 ($927.36)

AIDS:

TC:$27648 ($30523.08), IC:$13008 ($14360.76), OC:$5880 ($6491.52), PC:$5640 ($6226.56), OtPC:$2580 ($2848.32), BHIC:$528 ($582.96)

**Quality:** medium

Classification: cost description

**Parkinson's Disease**

**Davis et al[62]**

2010

US

To assess the extent to which patients diagnosed with Parkinson's disease are non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.

**Design:** retrospective administrative claims study

**Follow Up:** 12 months

**Sample Size:** 3119 (A:1211, NA:1908)

**Measure:** MPR

**Classification:**

(≥80% = adherent, <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Total costs**

<table>
<thead>
<tr>
<th>Pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical costs</td>
</tr>
</tbody>
</table>

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2001

**Cost of Nonadherence:**

HIV:

TC:$18511 ($24262.36), PC:$2684 ($3537.36), MC:$15827 ($20859.12)

**Quality:** medium

Classification: cost outcome description

**Delea et al[63]**

To assess the

**Design:** retrospective

**Measure:** PDC

**Total costs**

<table>
<thead>
<tr>
<th>Type of Costs: adjusted and unadjusted</th>
</tr>
</thead>
</table>

**Quality:** high
2011 US associations between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilisation and costs.

**Historical cohort study**

**Follow Up:** 12 months

**Sample Size:** 1215 (A:617, NA:598)

**Classification:**

(\geq 80\% = satisfactory, <80\% = unsatisfactory)

**Method of Assessment:** pharmacy claims data

**Inpatient costs:**

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2005

**Cost of Nonadherence:**

Adjusted all cause:

TC:$19686 ($23625.30),

IC:$5954 ($7145.43),

PC:$6391 ($7669.88),

OC:$8795 ($10554.94)

Adjusted disease state specific:

TC:$8574 ($10289.71),

IC:$3705 ($4446.39),

PC:$3850 ($4620.41),

OC:$1884 ($2261)

Unadjusted all cause:

TC:$19362 ($23236.46),

IC:$5463 ($6556.18),

PC:$6158 ($7390.26),

OC:$7740 ($9288.82)

Unadjusted disease state specific:

TC:$9156 ($10988.18),

IC:$3238 ($3885.94),

PC:$3789 ($4547.20),

OC:$2129 ($2555.03)

**Wei et al[64] 2014 US** To examine the associations of adherence to antiparkinson drugs with healthcare utilisation and economic outcomes.

**Design:** retrospective cross-sectional study

**Follow Up:** 19 months

**Sample Size:** 7583 (90-100\%:3948, 80-89\%:1456, \leq 79\%:2179)

**Measure:** MPR

**Classification:**

(\geq 90\% = high, >80\% < 90\% = moderate, \leq 80\% = low)

**Method of Assessment:** pharmacy claims data

**Total costs**

**Inpatient costs**

**Outpatient costs**

**Pharmacy costs**

**Classification:**

**Cost of Nonadherence:**

Adjusted all cause:

TC(90-100):$36407 ($41293.43),

TC(80-89):$43417 ($49244.29),

TC(\leq 79):$45867 ($52023.13),

IC(90-100):$15294 ($17346.71),

IC(80-89):$21603 ($2555.03)

**Quality:** medium
Musculoskeletal

Ivanova et al[65]

2012 US

To compare the rates of severe relapse and total direct and indirect costs over a 2 year period between US based employees with MS who were adherent and non-adherent to disease modifying drugs.

**Design:** retrospective cohort study

**Follow Up:** 2 years

**Sample Size:** 648 (A:448, NA:200)

**Measure:** MPR

**Classification:**

(≥80% = adherent, <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Total costs**

Total healthcare costs

Inpatient costs

Outpatient costs

ED costs

Pharmacy costs

Medical costs

Short term disability costs

Absenteeism cost

**Type of Costs:** unadjusted

**Classification:** all cause, disease state specific and indirect

**Currency Year:** USD, 2007

**Cost of Nonadherence:**

All cause:

TC:$8079 ($9276.76),

THC:$6022 ($6830.25),

IC:$1030.50 ($1168.81),

OC:$3231 ($3664.65),

EDC:$143.50 ($162.76),

PC:$1617 ($1834.03),

MC:$4405.50 ($4996.79)

Disease state specific:

TC:$3005 ($3408.32),

IC:$505 ($572.78),

OC:$1710 ($1939.51),

EDC:$37 ($41.97),

PC:$753 ($854.07),

MC:$2252 ($2554.26)

Indirect:

STDC:$1231 ($1396.22),

Absence cost:

AbC:$826 ($936.86)

**Quality:** high

**Classification:** cost outcome description

---

Tan et al[66]

2011

To assess the impact of treatment adherence

**Design:** retrospective cohort study

**Measure:** MPR

**Classification:**

Medical costs

**Type of Costs:** adjusted and unadjusted

**Classification:** disease state specific

**Quality:** medium

**Classification:** cost outcome description
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>2007</td>
<td>US</td>
<td>Retrospective observational cohort analysis</td>
<td>12 months</td>
<td>5435 (A:1744, NA:3691)</td>
<td>MPR</td>
<td>≥95% = very high, &gt;90&lt;95% = high, 50-90% = intermediate, &lt;50% = low</td>
<td>TH(≥95):$42250 ($52330.90), TH(90-95):$39236 ($48597.76), TH(50-90):$54770 ($67838.19), TH(&lt;50):$131357 ($162698.93), IC(≥95):$1156 ($1431.82), IC(90-95):$1362 ($1686.97), IC(50-90):$19096 ($23652.33), IC(&lt;50):$81572 ($101035.18),</td>
<td>high</td>
</tr>
<tr>
<td>Wu et al[69] 2010 US</td>
<td>To examine the association between adherence with imatinib and direct healthcare costs and resource utilisation</td>
<td>Design: retrospective observational cohort analysis</td>
<td>Measure: MPR</td>
<td>Total costs</td>
<td>Type of Costs: unadjusted Classification: disease state specific</td>
<td>Quality: medium Classification: cost description</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Method of Assessment: pharmacy claims data</td>
<td></td>
<td>Method of Assessment: pharmacy claims data</td>
<td>Outpatient costs</td>
<td>Cost of Nonadherence:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ED costs Pharmacy costs</td>
<td>TC:$107341 ($119415.73),</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other pharmacy costs</td>
<td>IC:$44498 ($49503.55),</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pharmacy costs Pharmacy costs</td>
<td>OC:$34097 ($37932.55),</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>EDC:$248 ($275.90),</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PC:$22846 ($25415.93),</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OtPC:$5652 ($6287.79)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The document presents data on healthcare costs including costs associated with different adherence levels:

- OC(≥95): $9299 ($11517.75)
- OC(90-95): $11148 ($13807.73)
- OC(50-90): $14631 ($18121.97)
- OC(<50): $33956 ($42057.94)
- EDC(≥95): $36 ($44.59)
- EDC(90-95): $568 ($703.53)
- EDC(50-90): $183 ($226.66)
- EDC(<50): $183 ($226.66)
- PC(≥95): $29056 ($35988.80)
- PC(90-95): $23693 ($29346.18)
- PC(50-90): $18330 ($22703.56)
- PC(<50): $8733 ($10816.70)
- OtPC(≥95): $2462 ($3049.44)
- OtPC(90-95): $2091 ($2589.92)
- OtPC(50-90): $2238 ($2771.99)
- OtPC(<50): $183 ($226.66)
- OtC(≥95): $241 ($298.50)
- OtC(90-95): $374 ($463.24)
- OtC(50-90): $371 ($459.52)
- OtC(<50): $5732 ($7099.66)
To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent members.

**Design:** retrospective cohort analysis
**Follow Up:** 12 months
**Sample Size:** 455
(A:146, NA:309)

**Measure:** MPR

**Classification:** (≥80% = adherent, <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Costs:**
- Inpatient costs
- Outpatient costs
- ED costs
- Pharmacy costs
- Medical costs

**Total healthcare costs**

**Cost of Nonadherence:**
- Adjusted:
  - THC:$49051 ($53503.88),
  - IC:$26470 ($28872.96),
  - OC:$14570 ($15892.67),
  - EDC:$4439 ($4841.98),
  - PC:$3581 ($3906.09)
- Unadjusted:
  - THC:$47868 ($52213.49),
  - IC:$26043 ($28407.20),
  - OC:$14173 ($15459.63),
  - EDC:$4058 ($4426.39),
  - PC:$3557 ($3879.91)

**Quality:** medium

**Classification:** cost description

To assess the relationship between medication adherence and healthcare costs among US patients on Metabolic conditions other than diabetes mellitus.

**Design:** retrospective cohort study
**Follow Up:** 12 months
**Sample Size:** 4923
(A:1372, NA:1304)

**Measure:** MPR

**Classification:** (≥80% = high adherent, <80% = low adherent)

**Type of Costs:** unadjusted

**Cost of Nonadherence:**
- Adjusted:
  - THC:$49051 ($53503.88),
  - IC:$26470 ($28872.96),
  - OC:$14570 ($15892.67),
  - EDC:$4439 ($4841.98),
  - PC:$3581 ($3906.09)
- Unadjusted:
  - THC:$47868 ($52213.49),
  - IC:$26043 ($28407.20),
  - OC:$14173 ($15459.63),
  - EDC:$4058 ($4426.39),
  - PC:$3557 ($3879.91)

**Quality:** medium

**Classification:** cost description
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Follow Up</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Quality</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Retrospective longitudinal</td>
<td>12 months</td>
<td>MPR</td>
<td>≥80% = adherent</td>
<td>Adjusted</td>
<td>Medium</td>
<td>cost description</td>
</tr>
<tr>
<td>Candielli et al [73]</td>
<td>Study</td>
<td></td>
<td></td>
<td>&lt;80% = nonadherent</td>
<td>All cause and disease state specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Retrospective observational</td>
<td>1527 days</td>
<td>MPR</td>
<td>classification:</td>
<td>All cause</td>
<td>Low</td>
<td>Cost outcome</td>
</tr>
<tr>
<td>Alvarez Payero et al [74]</td>
<td>Study</td>
<td></td>
<td>MPR</td>
<td>Pharmacy records</td>
<td>unadjusted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Method of Assessment:** Pharmacy claims data

**Pharmacy costs:**

**Other pharmacy costs:**

**Total costs:**

**Type of Costs:** adjusted

**Cost of Nonadherence:**

**Quality:** medium
<table>
<thead>
<tr>
<th>Spain</th>
<th>hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.</th>
<th>Sample Size: 87 (A:21, NA:66)</th>
<th>(&gt;75% = adherent, ≤75% = nonadherent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of Assessment: pharmacy and hospital claims data</td>
<td>Cost of Nonadherence####: description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause:</td>
<td>HC:€6275.80 ($8893.94)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group; ": extrapolated annual cost and subgroups averaged; ": cost represents losses in workplace productivity; ": negative value as costs modelled against adherent group; ####: cost per episode of nonadherence


<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td></td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>4</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>4</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>5</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>5</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>5</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>5</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>5</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>5-6</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>5-7</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>6-7</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>n/a</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td>6-7</td>
</tr>
<tr>
<td>Section/topic</td>
<td>#</td>
<td>Checklist item</td>
<td>Reported on page #</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---</td>
<td>--------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
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Economic impact of medication nonadherence by disease groups: a systematic review

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Title Page

Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in March 2017. Studies quantifying the cost of medication nonadherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy five individual studies assessing the cost of medication nonadherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of nonadherence per person ranged from $949-$53,504 (in 2015 US dollars). Costs attributed to “all causes” nonadherence ranged from $5,271 to $52,341. Medication possession ratio was the metric most utilized to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (81% of studies), pharmacy costs (72%), inpatient costs (51%), outpatient costs (51%), emergency department visit costs (30%), medical costs (27%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338
Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication nonadherence via quantifying the cost of medication nonadherence across different disease groups.
- A large comprehensive review – 2,692 citations identified, 75 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.
1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources. [2]. Medications are a cost-effective treatment modality[3], but intentional and unintentional inappropriate medication use by patients is common, mostly through differing degrees of adherence termed medication nonadherence. Medication adherence is defined as ‘the extent to which the patients’ behavior matches agreed recommendations from the prescriber’, emphasising the importance on the patients’ decisions and highlighting the modifiable aspect of nonadherence[4].

With estimates of 50% nonadherence to long term therapy for chronic illnesses[5], efforts to improve medication adherence represent an opportunity to improve health outcomes and health system efficiency. The clinical, economic and human consequences of medication nonadherence pose significant burdens. Estimates of the costs range from US$100-$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A$7 billion[8 9] in Australia. As well as substantially increasing healthcare costs, nonadherence compromises the effective use of medicines, can decrease patients’ quality of life, increases the risk of medication misadventures, can lead to poor health outcomes, and can result in preventable hospitalizations[10]. Ten percent of hospitalizations in older adults are attributed to medication nonadherence [11 12] with the typical nonadherent patient requiring three extra medical visits per year leading to $2000 increased treatment costs per annum[13]. In diabetes the estimated costs savings associated with improving medication nonadherence range from $661 million to $1.16 billion [14]. Nonadherence is thus a critical clinical and economic problem[5].

An understanding of the economic impact of medication nonadherence on the healthcare system can influence health policy. While the cost of nonadherence for some disease groups has already been analyzed with varying findings, no systematic reviews provide a holistic and comparative picture across disease groups. Policymakers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[15]. However there is still a budgetary problem that needs to be considered. Quantifying the cost of medication nonadherence is a necessary element to allow valuable correlation between healthcare resource use associated with higher disease prevalence and costs associated with medication nonadherence to be drawn. The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the...
literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.
2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[16].

2.1 Search strategy and selection criteria

A literature search was conducted in March 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB]) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[17] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-
group analysis and statistical significance), conclusions and miscellaneous (funding source, references to other relevant studies, limitations and reviewers comments).

Costs were defined as any indicator associated with medication nonadherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients' families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [18], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[18]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [19]. All studies were classified in accordance with Drummond’s distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).

The Drummond checklist [20] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least 75% of Drummond’s criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

Outcome/indicator costs were independently extracted utilising predesigned data extraction forms (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs, emergency department costs, and hospitalisation costs) for the purpose of integrating the findings on the cost of medication nonadherence to pool data and increase the power of analysis.
3 Results

3.1 Study Selection

Search strategies retrieved 2692 potential articles after duplicates were removed. Two hundred and seventy four articles were selected for full text review. Seventy five studies were included in the review (Figure 1).

3.2 Characteristics of individual studies

Sixty-two studies (82%) were conducted in the United States[11 21-81], four in Europe[82-85], four in Asia[86-89], three in Canada[90-92], one in the United Kingdom[93] and one across multiple countries throughout Europe and the United Kingdom[94]. Publication years ranged from 1997 to 2016. Individual studies reported a large variety of costs, calculated by varying means. Forty-two studies (56%) reported unadjusted costs[21 25 26 29 31-35 37-42 45 47-49 51-55 57 62-67 71 74 80 81 83-85 87-89 94], 19 (25%) adjusted costs[11 22-24 28 30 43 50 56 58-60 70 72 75-77 82 86], 11 a combination of adjusted and unadjusted[27 36 44 46 61 68 69 73 78 79 92], two unadjusted and predicted[90 91] and one predicted costs[93]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy claims data (87%)[11 21-28 30-51 54 56 58-83 87-92]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data, disease state specific recommended guidelines and health claims data. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 49 studies (65%) reporting nonadherence based on this measure[23 24 27 28 31-35 39-43 45 46 48-50 54 56 57 59-63 66-77 80-83 87-92]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (9%)[30 36 44 47 51 78 79], with all other studies utilizing an array of measures including self-report[93], urine testing[55], observational assessment[94], time to discontinuation[58], cumulative possession ratio[22], disease specific medication management guidelines[65 84], Morisky 4-Item scale[52], medication gaps[37], prescription refill rates[21 26] and medication supplies[11]. The main characteristics of the included studies are summarised in eTable 2.
3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[32 36 39 49 50 56 70 74 82 88], 56 of medium[11 21-25 27-31 33-35 37 38 40-47 52-55 57 58 60-63 65 66 68 69 71 72 75-81 83 86 89-94] and nine of low quality[26 48 59 64 67 73 85 87]. Scores ranged from 26.1% to 87.5% (mean 62.9%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [70]. The item ‘the choice of discount rate is stated and justified’ was applicable only to studies covering a time period of more than one year; all studies that cover more than one year failed to identify or explain why costs had not been discounted. Details of the analysis and interpretation of results were lacking in the majority of studies resulting in medium or low quality scores.

Through utilisation of Drummond’s distinguishing characteristics of healthcare evaluations criteria[19] it is apparent that no full economic evaluation was conducted in any of the included studies. All studies performed partial economic evaluations of varying extents. The classification of economic evaluations resulted in 55 cost description studies (73% of those included), 15 cost outcome descriptions and five cost analysis studies (eTable 2).

3.4 Medication nonadherence and costs

The cost analysis of studies (figure 2 and figure 3) reported annual medication nonadherence costs incurred by the patient per year. The adjusted total cost of nonadherence across all disease groups ranged from $949 to $53,504, while the unadjusted total cost ranged from $669 to $162,699. Figure 2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by patients across disease groups where three or more studies were included for review. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Many different indicators were used to estimate medication nonadherence costs with no clear definition of what was incorporated in each cost component. The composition of included costs to estimate total cost or total healthcare cost varied significantly between studies thus indicators were grouped for analysis based on the original studies classification of the cost. The main ones were total cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (47%), medical costs (29%), emergency department costs (28%), and hospitalization costs (18%) (eTable 2). Avoidable costs (e.g., unnecessary hospitalisations, physician office visits and healthcare resource utilization) were not well defined with majority of studies failing to quantify these costs.
Lower levels of adherence across all measures (e.g., MPR, PDC) were generally associated with higher total costs. From those that reported total or total healthcare costs, 37 studies (50%) reported nonadherence costs to be greater than adherence costs[23 24 26 28 30 31 33 36-38 41 42 46 48 49 54 55 57 60-64 69-77 82 91-94] and 11 studies (15%) reported nonadherence costs to be less than adherence costs[22 25 35 43 58 62 65 80 87 89 90]. Four reported fluctuating findings based on varying nonadherence cost subcategories[32 47 66 88] and two studies reported conflicting findings between adjusted and unadjusted costs [78 79]. Sunyecz et al[67], Eisenberg et al[40] and Joe et al[86] reported all cause total nonadherence costs to be higher ($28,395 vs. $24,134, $7,551 vs. $7,051 and $5,271 vs. $4,375) but disease group specific nonadherence costs to be lower ($1923 vs. $3273, $703 vs. $1012 and $3,252 vs. $4,151) whereas Hansen et al[46] reported all cause total nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

The association between nonadherence and cost was determined through use of a variety of scaling systems. The most utilized methods were MPR and PDC. These measures could then further be subcategorized based on the percentage of adherence/nonadherence. The 80-100% category was classified as the most adherent group across both scales, with the most common definition of nonadherence being <80% MPR or PDC.

3.5 Cost of medication nonadherence via disease group

Cancer exhibited more than double the cost variation of all other disease groups ($114,101). Osteoporosis ($43,240 vs. $42,734), diabetes mellitus ($7,077 vs. $6,808) and mental health ($16,110 vs. $23,408) cost variations were similar between adjusted and unadjusted costs while cardiovascular disease adjusted costs were more than double unadjusted costs ($16,124 vs. $6,943). Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy and parkinson’s disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal conditions. Direct costs had greater economic bearing than indirect costs across all disease groups.

3.5.1 Cardiovascular Disease

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [11 23 30 60 61 64 66 75 80 88 90 91]. Six studies reported adjusted costs [11 23 30 60 61 75] with annual costs being extrapolated for two of these[30 60]. Total healthcare costs and/or total...
costs were assessed in all of the studies with the major indicators measured including pharmacy costs [11 30 60 61 75], medical costs [11 23 30 60 75] and outpatient costs [30 61]. The annual economic cost of nonadherence ranged from $3,347 to $19,472. Sokol et al [11] evaluated the economic impact of medication nonadherence across three cardiovascular conditions; hypertension, hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined, pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups. Total costs and medical costs were lower for the adherent groups of hypertension and hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.

Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total costs of nonadherence ranging from $1,433 to $8,377 [64 66 80 88 90 91]. Rizzo et al [64] reported cost findings through subgroup analysis of five conditions. For all conditions the total healthcare costs were higher for nonadherent groups compared with adherent. While Zhao et al [80], categorized participants into adherence subgroups; finding that total healthcare costs were lower for the nonadherent population. The remaining studies used five key indicators to determine the economic impact: inpatient costs [66 88], outpatient costs [66 88], pharmacy costs [66 90 91], medical costs [90 91] and hospitalization costs [90 91].

### 3.5.2 Mental Health

The analyses used to report the economic impact of medication nonadherence in mental health varied widely. Eleven of 14 studies provided a total nonadherence cost estimate in mental health [22 24 26 51 58 65 72 81 86 93 94], with annual cost data being extrapolated for four of these [26 65 81 94]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from $3,252 to $19,363 [22 24 58 59 72 86]. Bagalman et al [24] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs while Robertson et al [81] highlighted the association between medication nonadherence and incarceration, with findings indicating incarceration and arrest costs are higher for worsening degrees of nonadherence. All other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication nonadherence were pharmacy costs [22 38 51 58 59 65 72 94], inpatient costs [38 59 65 93 94], outpatient costs [22 38 58 65 94] and hospitalization costs [21 22 58 94].

The total unadjusted cost for medication nonadherence ranged from $2,512 to $25,920 as reported in four studies [51 65 81 94]. Becker et al [26] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%,...
<25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al[93] outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

### 3.5.3 Diabetes mellitus:

Nine studies reported some cost measurement of the impact of medication nonadherence with reference to the health system and the individual[39 44 50 73 75 87 89 92]. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion[50]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819 [46 50 73 75 92]. One study reported total costs in relation to subgroup analysis based on MPR level[73], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients[75].

A further three studies reported unadjusted cost findings[39 87 89] and four studies reported unadjusted costs in addition to adjusted values[44 46 73 92]. Unadjusted total healthcare costs and/or total costs ranged from $1,142 to $7,951. Extrapolated annual costs were determined for two studies based on cost data presented [39 89].

The most prominent indicators used to determine costs were pharmacy costs[39 44 46 73 75 92], outpatient costs[39 46 75 89 92], inpatient costs[46 75 92] and hospitalization costs[50 87 89]. All studies assessed the direct costs associated with medication nonadherence. One study evaluated the relationship between nonadherence and short term disability costs in addition to assessing direct costs[44].

### 3.5.4 Osteoporosis:

The cost of medication nonadherence in relation to osteoporosis was predominately examined through analysis of the direct costs associated with nonadherence using total healthcare costs and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department costs. Two studies further assessed the economic impact of nonadherence through evaluation of fracture related costs [47 83]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [27 78 79 82]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[27] using MPR 20% interval...
increases and the two studies conducted by Zhao et al[78 79] using PDC, with ≥80% classified as high adherence, 50-79% medium adherence and <50% low adherence. In the studies conducted by Zhao et al[78 79], total healthcare costs were highest for the medium adherence group ($41,402 and $44,190) followed by the highest adherence group ($37,553 and $43,863), and lowest for the low adherence group ($34,019 and $43,771). These annual costs were extrapolated from study data. In contrast, Briesacher et al[27] modelled the subgroup analyses against the lowest adherence group (<20% MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from $669 to $43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In the three studies that reported the lowest level of nonadherence to be PDC <50%, the cost of this category ranged from $16,938 to $43,404 [47 78 79].

One study examined only the medical costs of nonadherence through MPR subgroup analysis in commercial and Medicare supplemental populations. The findings were that, for all levels of nonadherence, costs of nonadherence were higher for Medicare supplemental patients [45].

3.5.5 Respiratory Disease:

All five studies reported the unadjusted cost of medication nonadherence. The methods of classifying adherence levels varied greatly among them[35 37 52 63 84]. Two studies used MPR[35 63], one the Morisky 4-Item scale[52], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[84] and one a 37 day gap in claims data[37]. Joshi et al[52] reported on the indirect costs of medication nonadherence through consideration of losses in total productivity costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs. Delea et al[35] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[63] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the lowest subgroup of adherence across all measures ranged from $804 to $36,259.

3.5.6 Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [43 56 70]. Of these, two reported the total cost ($12,085 and $37,151)[43 70] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).
The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs [29 53]. Carter et al [29] reported hospitalization costs to be $42,854 while Kane et al [53] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

3.5.7 Epilepsy:

Three studies reported the economic impact of medication nonadherence in epilepsy. They all reported unadjusted costs using an MPR cut off of <80% [34 41 42]. The main economic indicators used to assess total costs were inpatient costs ($2,289 to $6,874), emergency department visit costs ($331 to $669) and pharmacy costs ($442 to $1,067). Davis et al [34] modelled the costs of the nonadherent group against the adherent group. The annual costs reported by Faught et al [42] were extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from $1,866 to $22,673.

3.5.8 HIV/AIDS:

The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all three studies was similar [25 31 62]. Two of the three studies examined the costs only for HIV [25 31], while Pruitt et al [62] assessed the cost in AIDS as well as HIV. The total unadjusted costs for nonadherent HIV patients ranged from $16,957 to $30,068 with one study further categorizing patients with HIV as having either a high viral load or low viral load [25]. The total cost of nonadherence in AIDS was $30,523 [62]. All studies used comparable indicators (total cost, inpatient cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.

3.5.9 Parkinson’s Disease:

The direct costs associated with Parkinson’s disease were assessed in all three studies. The unadjusted total cost ranged from $10,988 to $52,023 [33 36 71]. Wei et al [71] further sub-grouped patients into MPR adherence percentage categories, and found that costs increased on all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that $10,290 could be attributed to medication nonadherence annually [36].

3.5.10 Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence [49], one assessed only the medical costs [68] and one examined the direct costs in...
commercial and Medicare supplemental patient populations[77]. Zhao et al[77] reported the adjusted annual cost in the commercial population to be $22,609, and in the Medicare supplemental group, $28,126. Ivanova et al[49] reported only unadjusted costs and the annual total cost of $3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

3.5.11 Cancer:

Two studies evaluated the effects of medication nonadherence in cancer[32 74]. One study reported total annual costs of $119,416[74], while the other gave a subgroup analysis based on classified adherence levels[32]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs ($162,699 and $67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

3.5.12 Addiction:

The adjusted annual total healthcare cost of medication nonadherence was reported as $53,504[55] while the unadjusted cost ranged from $29,406 to $52,213 [55 69]. Leider et al[55] reported the main contributors to this cost to be outpatient costs ($10,829) and pharmacy costs ($8,855), whereas Tkacz et al[69] reported them to be inpatient costs ($28,873 and $28,407) and outpatient costs ($15,893 and $15,460).

3.5.13 Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of $138,525[54]. The economic indicators used to derive this cost were inpatient costs ($16,192), outpatient costs ($111,100), emergency department visit costs ($801) and pharmacy costs ($3,538).

3.5.14 Blood conditions:

Only Candrilli et al[28] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of $13,458 for nonadherence classified as MPR <80%.

3.5.15 All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of
these studies, annual costs were extrapolated from the original data\[30 46 49 60 63 65 94\]. Ten studies reported on economic indicators without giving total cost or total healthcare cost\[21 44 45 53 54 56 59 80 85 94\], and one study reported on costs per episode of nonadherence\[85\].

The adjusted cost of medication nonadherence was reported in 10 studies with an estimated range of $7,808 to $52,341 \[11 28 30 36 46 58 60 70 75 76\]. Sokol et al\[11\] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al\[60\] reported only using MPR level breakdown.

Fourteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of $1,037 to $53,793 \[21 40 45 49 53 54 57 63-65 67 80 85 94\]. A further four studies reported adjusted and unadjusted costs\[36 44 46 92\]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).

### 3.6 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of required statistical parameters in particular standard deviation\[95\]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.
4 Discussion

This systematic review broadens the scope of knowledge associated with the economic impact of medication nonadherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication nonadherence. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, Emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesise costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication nonadherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to nonadherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to
medication nonadherence thus enabling greater planning in terms of health policy to help counteract costs.

The economic, clinical and humanistic consequences of medication nonadherence will continue to grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to adequately address the determinants of adherence through utilization of effective health interventions. Haynes et al [96] highlights that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments”. Improving medication adherence provides an opportunity for major cost savings to healthcare systems. Moving forward health policy needs to recognize the link between adherence and health system efficacy and the opportunity it presents to allocate health budget spending more appropriately. Predictions of population health outcomes through utilization of treatment efficacy data need to be used in conjunction with adherence rates to inform planning and project evaluation[5]. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [97], who compared six key adherence measures on the same study participants, found that the measures produced similar adherence values for all participants, although PDC and continuous measure of medication gaps produced slightly lower values. While this highlights the comparability of the measures of medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 65% of studies, followed by PDC, which was used in 9%. These percentages were consistent with those found recently by Sattler et al [98]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[90] defined MPR as the total days’ supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[75] removed the number of hospitalized days from the calculation; and Pittman et al[60] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Twenty-eight studies defined nonadherence as MPR< 80%, and 19
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
conclusions that are able to be drawn and emphasised the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al.[101] highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Of the seventy five included studies, sixty two of the studies were conducted in the United States. Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and disease states. Comparison of costs between healthcare systems is difficult as no two are the same and as healthcare is generally more expensive in the United States cost estimates may not reflect average values. Thus caution needs to be taken when interpreting results however findings help to represent the significance of the economic burden medication nonadherence plays. Analysis of studies not conducted in the United States support the finding that generally medication nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[21 22 64 72 73 93]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.
5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However, differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilisation of existing data could help to better define costs and provide valuable input into the development of an economic model to standardise the economic impact of medication nonadherence.
6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data
eextraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All
other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and
modified the drafts. All authors read and approved the final manuscript.

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or not-for-profit sectors.

Competing interests: None declared

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material.

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72. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003; 11(12):817-22 doi: 10.2165/00115677-200311120-00006[published Online First: Epub Date]


87. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;49:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]].


Figure Legends

Figure 1: PRISMA Flow Diagram
The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2692 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication nonadherence using original cost data. Intervention studies were required to report baseline data. Seventy five original studies met the inclusion criteria.

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
Encompass the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 1: Annual Unadjusted Medication Nonadherence Costs per patient per year
Encompass the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.
Figure 1: PRISMA Flow Diagram

209x297mm (300 x 300 DPI)
**Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year**

*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.**

All cause costs: mixed disease state studies

209x297mm (300 x 300 DPI)
Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year *Disease groups with three or more studies were included. Epilepsy only included three studies limiting the range of costs.** All cause costs: mixed disease state studies

209x297mm (300 x 300 DPI)
## eTable 1 Search Strategy

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<th>Database</th>
<th>Search Strategy</th>
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<tr>
<td>Scopus</td>
<td>(TITLE-ABS-KEY ( medication AND compliance OR patient AND compliance ) ) AND (TITLE-ABS-KEY ( statistical AND model ) ) AND (TITLE-ABS-KEY ( health AND care AND cost ) )</td>
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</table>
eTable 2: Studies identified with costs reported by adherence level and disease state

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Objective</th>
<th>Study Characteristics</th>
<th>Adherence (as reported in paper)</th>
<th>Outcomes/Indicators</th>
<th>Results (USD, 2015)</th>
<th>Quality</th>
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<tr>
<td>Aubert et al[1] (2010, US)</td>
<td>To investigate whether compliance during the first 2 years of statin therapy is associated with reduced hospitalization rates and direct medical costs during year 3.</td>
<td>Design: Retrospective cohort study, Follow Up: 3 years, Sample Size: 10227 (A:3512, NA:6715)</td>
<td>Measure: MPR Classification: MPR &lt; 80 = non-compliant</td>
<td>Total Healthcare costs, Medical Costs</td>
<td>Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence: THC:$5289.61 ($6865.90), MC:$4908.09 ($6370.60)</td>
<td>medium</td>
</tr>
</tbody>
</table>
Dragomir et al\[4\]  
2010 Canada  
To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalization costs.  
**Design:** Retrospective cohort study  
**Follow Up:** 3 years  
**Sample Size:** 56896 (A:38217, NA:18679)  
**Measure:** MPR  
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent  
**Method of Assessment:** pharmacy claims data  
**Type of Costs:** unadjusted and predicted  
**Classification:** disease state specific and hospitalised patients  
**Currency Year:** CAD, 2006  
**Cost of Nonadherence:**  
Disease state specific: THC:$7165 ($6900.87), PC: $1800 ($1733.64), MC: $1370 ($1319.50), HC: $3995 ($3847.73)  
Unadjusted Hospitalised patients:  
THC: $17397 ($16755.67), PC: $2685 ($2586.02), MC: $2608 ($2511.86), HC: $12104 ($11657.79)  
Predicted disease state specific:  
HC:$3877 ($3734.08)  
Predicted hospitalised patient:  
HC:$11715 ($11283.13)  
**Quality:** medium  
**Classification:** cost description

Dragomir et al\[5\]  
2010 Canada  
To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.  
**Design:** Retrospective cohort study  
**Follow Up:** 3 years  
**Sample Size:** 55134 (A:28549, NA:26585)  
**Measure:** MPR  
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent  
**Method of Assessment:** pharmacy claims data  
**Type of Costs:** unadjusted and predicted  
**Classification:** disease state specific and hospitalised patients  
**Currency Year:** CAD, 2005  
**Cost of Nonadherence:**  
Disease state specific: THC:$6243 ($6175.76), PC:$2506 ($2479.01), MC:$2608 ($2511.86), HC: $2496 ($2469.12)  
Unadjusted Hospitalised patients:  
THC: $14728 ($14566.40), PC: $3374 ($3337.66), MC: $2475 ($2448.34), HC: $8876 ($8780.40)  
Predicted disease state specific:  

**Type of Costs:** unadjusted and predicted  
**Classification:** disease state specific and hospitalised patients  
**Currency Year:** CAD, 2005  
**Cost of Nonadherence:**  
Disease state specific: THC:$6243 ($6175.76), PC:$2506 ($2479.01), MC:$2608 ($2511.86), HC: $2496 ($2469.12)  
Unadjusted Hospitalised patients:  
THC: $14728 ($14566.40), PC: $3374 ($3337.66), MC: $2475 ($2448.34), HC: $8876 ($8780.40)  
Predicted disease state specific:  
**Quality:** medium  
**Classification:** cost description
To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.

**Design:** Retrospective cohort study

**Follow Up:** 18 months

**Sample Size:** 381422 (A:258013, MA:65795, LA:57614)

**Measure:** MPR

**Classification:**
- MPR ≥ 80 = adherent
- MPR >60<79% = moderate adherence
- MPR <59 =low adherence

**Method of Assessment:** pharmacy claims data

**Type of Costs:**
- Total Healthcare Costs
- Pharmacy Costs
- Medical Costs

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2009

**Cost of Nonadherence:**
- all cause:
  - THC(>80):$6798.67 ($7505.66),
  - THC(60-79):$7072.67 ($7808.16),
  - THC(<59):$7401.33 ($8170.99),
  - PC(>80):$1767.33 ($1951.11),
  - PC(60-79):$1789.33 ($1975.40),
  - PC(<59):$1937.33 ($2138.79),
  - MC(>80):$4472.67 ($4937.78),
  - MC(60-79):$4840.67 ($5344.05),
  - MC(<59):$5138.67 ($5673.04)

**Disease state specific:**
- PC(>80):$558.67 ($616.77),
- PC(60-79):$442.67 ($488.70),
- PC(<59):$325.33 ($359.16),
- MC(>80):$1596.67 ($1762.71),
- MC(60-79):$1722 ($1901.07),
- MC(<59):$1792.67 ($1979.09)

**Quality:** medium

---

To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and

**Design:** Retrospective cohort study

**Follow Up:** 2 years

**Sample Size:** 625620 (A:467006, MA:96226, LA:62388)

**Measure:** MPR

**Classification:**
- MPR ≥ 80 = adherent
- MPR >60<79% = moderate adherence
- MPR <59 =low adherence

**Type of Costs:**
- Total Healthcare Costs
- Outpatient Costs
- ED Costs
- Pharmacy Costs
- Hospitalization Costs

**Classification:** disease state specific

**Currency Year:** USD, 2008

**Cost of Nonadherence:** Adjusted:
- THC(>80):$7761 ($8077.79),
- THC(60-79):$7672.67 ($8377.05),
- THC(<59):$7370 ($8199.05),
- PC(>80):$390 ($3771.34),
- PC(60-79):$3705 ($4121.77),

**Quality:** medium
To investigate variations in compliance with four classes of antihypertensive agents—diuretics, ACEIs, CCBs and β-

| Design: Retrospective cohort study Follow Up: 12 months Sample Size: 7211(P:2668, NC:3101, NP:649, T:793) | Measure: ordinary least square regression analysis Classification: >80% = persistent, ≥30<80% = non-compliance, <30% Total Healthcare Costs |
| Costs | |
| Quality: low Classification: cost description |

To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

**Sokol et al**[9] 2005 US

**Design:** Retrospective cohort observational study  
**Follow Up:** 12 months  
**Sample Size:** 137277  
** Measure:** medication supply  
**Classification:** 1-19%, 20-39%, 40-59%, 60-79%, 80-100%  
**Method of Assessment:** pharmacy claims data  

**Type of Costs:** adjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 1998  
**Cost of Nonadherence:** All cause:  
- Diabetes:  
  - TC(1-19): $16498 ($23071.58)  
  - TC(20-39): $13077 ($18287.49)  
  - TC(40-59): $12978 ($18149.05)  
  - TC(60-79): $11484 ($16059.77)  
  - TC(80-100): $8886 ($12426.60)  
  - PC(1-19): $3312 ($1834.76)  
- Hypertension:  
  - TC(1-19): $175 (2618.55)  
  - TC(20-39): $1711 ($2557.27)  
  - TC(40-59): $1752 ($2618.55)  
  - TC(60-79): $1752 ($2618.55)  
  - TC(80-100): $1752 ($2618.55)  
  - PC(1-19): $3312 ($1834.76)  

**Total Costs:**  
- Pharmacy Costs:  
  - Diabetes:  
    - THC(≥80): $3190.98  
    - THC(30-80): $3718.58  
    - THC(<30): $3779.86  
  - Hypertension:  
    - THC(≥80): $2135 ($3190.98)  
    - THC(30-80): $2488 ($3718.58)  
    - THC(<30): $2529 ($3779.86)  
  - Angina:  
    - THC(≥80): $1358 ($2029.67)  
    - THC(30-80): $1711 ($2557.27)  
    - THC(<30): $1752 ($2618.55)  
  - Diabetes:  
    - THC(≥80): $770 ($1150.85)  
    - THC(30-80): $1123 ($1678.44)  
    - THC(<30): $1164 ($1739.72)  
  - CHF:  
    - THC(≥80): $698 ($1043.23)  
    - THC(30-80): $1051 ($1570.83)  
    - THC(<30): $1092 ($1632.11)  
  - Angina:  
    - THC(≥80): $702 ($1049.21)  
    - THC(30-80): $1055 ($1576.81)  
    - THC(<30): $1096 ($1638.09)  

**Quality:** medium  
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<td>MC(40-59)</td>
<td>$24103 ($33706.77)</td>
<td>$6522 ($9120.67)</td>
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<tr>
<td>MC(60-79)</td>
<td>$26373 ($36881.24)</td>
<td>$6291 ($8797.63)</td>
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<tr>
<td>MC(80-100)</td>
<td>$19056 ($26648.81)</td>
<td>$54570 ($6390.90)</td>
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</tbody>
</table>

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For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patient with complicated and uncomplicated hypertension and to

Design: Retrospective cohort study
Follow Up: 3.3 years
Sample Size: 15206 (not specified)

Measure: MPR
Classification: MPR<80 = undersupply, MPR >120 = oversupply
Method of Assessment: pharmacy claims data

Total Healthcare Costs
- Inpatient Costs
- Outpatient Costs
- Pharmacy Costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2002
Cost of Nonadherence:
- THC:$6032.5 ($7830.11)
- IC:$2067 ($2682.94)
- OC:$3965 ($5146.52)
- PC:$130 ($168.74)

Quality: medium
Classification: cost description
### Wu et al [11]

2011  
US

To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.

**Design:** Retrospective cohort study  
**Follow Up:** 1 year  
**Sample Size:** 1705 (A:624, NA:1081)

**Measure:** MPR  
**Classification:** MPR≥80 = adherent, MPR <80 = nonadherent  
**Method of Assessment:** pharmacy claims data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Total Healthcare Costs</th>
<th>Type of Costs: adjusted</th>
<th>Quality: medium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmacy Costs</td>
<td>Classification: all cause and disease state specific</td>
<td>Classification: cost description</td>
</tr>
<tr>
<td></td>
<td>Medical Costs</td>
<td>Currency Year: USD, 2005</td>
<td>USD, 2005</td>
</tr>
<tr>
<td>Total</td>
<td>THC:$17807 ($21370.30), PC:$4915 ($5898.52), MC:$12892 ($15471.77)</td>
<td>Cost of Nonadherence: all cause: THC:$2789 ($3347.10), PC:$489 ($586.85) MC:$2300 ($2760.25)</td>
<td></td>
</tr>
</tbody>
</table>

### Zhao et al [12]

2014  
US

To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.

**Design:** Retrospective cohort study  
**Follow Up:** 1 year  

**Measure:** MPR  
**Classification:** <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%  
**Method of Assessment:** pharmacy claims data, census data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Total Healthcare Costs</th>
<th>Type of Costs: unadjusted</th>
<th>Quality: medium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmacy Costs</td>
<td>Classification: all cause and disease state specific</td>
<td>Classification: cost description</td>
</tr>
<tr>
<td></td>
<td>Medical Costs</td>
<td>Currency Year: USD, 2010</td>
<td>USD, 2010</td>
</tr>
<tr>
<td>Total</td>
<td>Cost of Nonadherence: all cause: PC(96-100):$2976.80 ($3247.04), PC(90-95):$2826.99 ($3083.63), PC(85-89):$2795.39 ($3049.16), PC(80-84):$2690.89 ($2935.17), PC(70-79):$2192.83 ($2391.90), PC(60-69):$2323.27 ($2534.18), PC(40-59):$2153.93 ($2349.47), PC(&lt;40):$1749.18 ($1907.97)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Disease state specific: THC(96-100):$6536.05 ($7129.40), THC(90-95):$6493.80 ($7083.31),</td>
<td></td>
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</tr>
</tbody>
</table>

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Mental Health

**Bagalman et al [13]**

2010 US

To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.

**Design:** Retrospective cohort study

**Follow Up:** 1 year

**Sample Size:** 1258 (A:444, NA:814)

**Measure:** MPR

**Classification:** MPR≥80 = adherent, MPR <80 = nonadherent

**Method of Assessment:** pharmacy claims data

**Total Costs**

**Type of Costs:**

- **Short term disability cost**
- **Workers compensation cost**
- **Paid time off cost**

**Cost of Nonadherence:**

- **TC:** $6894 ($8273.53)
- **STDC:** $2134 ($2561.03)
- **WCC:** $762 ($914.48)
- **PTOC:** $3998 ($4798.03)

**Quality:** medium

**Classification:** cost description

**Currency Year:** USD, 2005

**Cost of Nonadherence:** TC:$6894 ($8273.53) STDC:$2134 ($2561.03) PTOC:$3998 ($4798.03)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objectives</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Total Costs</th>
<th>Type of Costs</th>
<th>Classification</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
</tr>
</thead>
</table>
adherence to treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.

Follow Up: 1 year
Sample Size: 1619
(<49%:388, 50-79%:259, 80-100%:664, >110%:308)

possession ratio Classification:
<49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers

Method of Assessment: pharmacy claims data

Sample Size: 1619
(49%:388, 50-79%:259, 80-100%:664, >110%:308)

Method of Assessment: pharmacy claims data

Cost of Nonadherence:

- TC: $8168 ($11261.74),
- OC: $3464 ($4776.04),
- PC: $1542 ($2126.05),
- HC: $3413 ($4705.72)

Hong et al [17]
2011
UK
To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.

Design: Prospective observational study
Follow Up: 21 months
Sample Size: 1341 (A:1024, NA:317)

Classification: adherent vs. nonadherent
Method of Assessment: observational assessment

Cost of Nonadherence:

- PC: £55.43 ($94.47)
- Disease state specific:
  - TC: £5846.29 ($9964.10)
  - OC: £1630.29 ($2778.58)
  - PC: £1082.86 ($1845.57)
  - HC: £337.14 ($574.60)

Jiang et al [18]
2015
US
To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization by controlling potential

Design: Retrospective cohort study
Follow Up: 2 years
Sample Size: 32374 (A:11642, NA:20732)

Classification: (PDC≥80% = adherent, PDC<80% = nonadherent)
Method of Assessment: observational assessment

Cost of Nonadherence:

- Disease state specific:
  - TC: $14141 ($14517.37)
  - PC: $3971 ($4076.69)
  - MSC: $10170 ($10440.68)

Quality: medium Classification: cost description

Quality: low Classification: cost description
To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.

**Joe et al [19]**

2016 South Korea

**Design:** Retrospective cohort study

**Follow Up:** 1 year

**Sample Size:** 7848 (A:2774, NA:2774, P:1956, NP:1956)

**Measure:** percentage of days of psychiatric prescription (PDP)

**Classification:**
- PDP≥80% = adherent,
- PDP<80% = nonadherent;
- persistent = continued medication without interruption ≥ 56 days, non-persistent = at least one medication interruption > 56 days

**Method of Assessment:** health insurance data

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2011

**Cost of Nonadherence:**
- All cause: TC:$4961 ($5271.40)
- Disease state specific: TC:$3061 ($3252.50)

**Quality:** medium

**Classification:** cost analysis

---

To assess the relative impact of non-adherence and other factors associated with resource use and costs incurred by people.

**Knapp et al [20]**

2004 UK

**Design:** Retrospective cohort study

**Follow Up:** 1 year

**Sample Size:** 658 (A:549, NA:109)

**Measure:** self-report

**Classification:**
- adherent vs. nonadherent

**Method of**

**Type of Costs:** predicted

**Classification:** disease state specific

**Currency Year:** GBP, 2001

**Cost of Nonadherence:**
- TC:£57580 ($116434.12)
- IC:£6714 ($13576.57)

**Quality:** medium

**Classification:** cost analysis
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offord et al[21]</td>
<td>2013</td>
<td>US</td>
<td>To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilisation and costs.</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>1462 (A:589, NA:873)</td>
<td>time to discontinuation</td>
<td>adherent vs. nonadherent</td>
<td>Pharmacy claims data</td>
<td>adjusted</td>
<td>USD, 2008</td>
<td>TC: $15400 ($17132.34), OC: $5773 ($6422.40), PC: $3777 ($4201.87), HC: $5850 ($6508.06)</td>
<td>medium</td>
<td>cost description</td>
</tr>
<tr>
<td>Offord et al[22]</td>
<td>2013</td>
<td>US</td>
<td>To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>354 (A:126, NA:228)</td>
<td>MPR ≥ 70= high adherence, MPR &lt; 70 = low adherence</td>
<td>Pharmacy claims data</td>
<td>adjusted</td>
<td>USD, 2008</td>
<td>IC: $9053 ($10071.37), PC: $4267 ($4746.99),</td>
<td>low</td>
<td>cost description</td>
<td></td>
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<tr>
<td>Robertson et al[23]</td>
<td>2014</td>
<td>US</td>
<td>To examine the impact of the combination of treatment utilization and medication possession on arrest and incarceration outcomes and on</td>
<td>Retrospective cohort study</td>
<td>90 days</td>
<td>1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)</td>
<td>MPR ≥80% = adherent</td>
<td>Medicaid claims data</td>
<td>unadjusted</td>
<td>USD, 2005</td>
<td>TC(90/90): $28068 ($33495.65), TC(60/90): $21720 ($25920.11), TC(30/90): $21084 ($25161.12)</td>
<td>medium</td>
<td>cost description</td>
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<tr>
<td>Case Management Costs</td>
<td>Pharmacy Costs</td>
<td>Psychiatric Assessment Costs</td>
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<tr>
<td>TC(0/90): $2516 ($14936.28)</td>
<td>IC(0/90): $12168 ($14520.99)</td>
<td>OC(90/90): $6468 ($7718.75)</td>
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<tr>
<td>TC(0/90): $6468 ($7718.75)</td>
<td>IC(60/90): $10068 ($12014.90)</td>
<td>OC(60/90): $4152 ($4954.89)</td>
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<tr>
<td>TC(0/90): $11376 ($13575.84)</td>
<td>IC(30/90): $592 ($6673.35)</td>
<td>OC(30/90): $2916 ($3479.88)</td>
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<tr>
<td>TC(0/90): $12516 ($14936.28)</td>
<td>IC(0/90): $6673.35</td>
<td>OC(0/90): $1200 ($1432.05)</td>
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<tr>
<td>TC(0/90): $12168 ($14520.99)</td>
<td>IC(90/90): $14936.28</td>
<td>OC(90/90): $2136 ($2549.05)</td>
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<td>IC(60/90): $12014.90</td>
<td>OC(0/90): $2136 ($2549.05)</td>
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<td>OC(60/90): $2136 ($2549.05)</td>
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<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson et al [24]</td>
<td>2006</td>
<td>US</td>
<td>Retrospective claims analysis</td>
<td>6 months</td>
<td>60386 (A:11526, NA:8860)</td>
<td>Antidepressant medication management measures</td>
<td>Inpatient costs, Outpatient costs, ED visit costs, Pharmacy costs, Physician office visit costs</td>
<td>unadjusted</td>
<td>all cause and disease state specific</td>
<td>medium</td>
<td>cost description</td>
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<tr>
<td>Svarstad et al [25]</td>
<td>2001</td>
<td>US</td>
<td>Retrospective database analysis</td>
<td>1 year</td>
<td>619 (A:413, NA:206)</td>
<td>quarter pharmacy claims classification: one or more quarters without a claim = nonadherent</td>
<td>Hospitalization costs</td>
<td>unadjusted</td>
<td>all cause and disease state specific</td>
<td>medium</td>
<td>cost description</td>
</tr>
<tr>
<td>White et al [26]</td>
<td>2003</td>
<td>US</td>
<td>Retrospective database analysis</td>
<td></td>
<td></td>
<td>MPR classification</td>
<td>Total costs Pharmacy</td>
<td>adjusted</td>
<td>disease state specific</td>
<td>medium</td>
<td>cost description</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
<td>Classification</td>
<td>Type of Costs</td>
<td>Cost of Nonadherence</td>
<td>Quality</td>
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<tr>
<td>US antidepressant treatment adherence among patients treated for depression</td>
<td>2017</td>
<td>US</td>
<td>Follow Up: 6 months</td>
<td>Sample Size: 14190 (A:5638, NA:8552)</td>
<td>MPR≥70% = adherent, MPR&lt;70% = nonadherent</td>
<td>Total costs</td>
<td>Medical costs</td>
<td>TC:$11815 ($16290.09), PC:$1123 ($1548.35), MC:$10692 ($14741.74)</td>
<td>medium</td>
<td></td>
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</tr>
<tr>
<td>Gentil et al[29]</td>
<td>2015</td>
<td></td>
<td>Design: Retrospective, observational cohort</td>
<td></td>
<td></td>
<td>Measure: MPR Classification:</td>
<td>Total costs</td>
<td>Inpatient costs</td>
<td>adjusted and unadjusted</td>
<td>medium</td>
<td></td>
</tr>
</tbody>
</table>
Canada adherence to oral antihyperglycemic agents and the effects of depression and anxiety disorders on these in older adults with type 2 diabetes analysis

Follow Up: 1 year
Sample Size: 301
(A:224, NA:77)

MPR≥80% = adherent,
MPR<80% = nonadherent

Method of Assessment:
pharmacy claims data

Outpatient state specific costs
Currency Year: CAD, 2010
Cost of Nonadherence:
Adjusted all cause:
TC:$11124 ($9818.67),
IC:$7419 ($548.43)
OC: $2687 ($2371.70),
PC: $504 ($444.86),
POC:$513 ($452.80)
Adjusted disease state specific:
TC:$4477 ($3951.65),
IC:$2836 ($2503.21)
OC: $1518 ($1339.87),
PC: $568 ($517.24)

Unadjusted all cause:
TC:$14979 ($13221.30),
IC:$6351 ($5605.75)
OC: $4058 ($3581.82),
PC: $3503 ($3091.94),
POC:$1066 ($940.91)

Unadjusted disease state specific:
TC:$9008 ($7950.97),
IC:$2854 ($2519.10)
OC: $2654 ($2342.57),
PC: $2498 ($2204.87),
POC:$1002 ($884.42)

To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/short term disability costs

Design: Retrospective, observational cohort analysis
Follow Up: 1 year
Sample Size: 4978
(A:2820, NA:2158)

Measure: PDC
Classification:
PDC≥80% = compliant,
PDC<80% = noncompliant

Healthcare costs
Type of Costs: adjusted and unadjusted
classification:
all cause and disease state specific
Currency Year: USD, 2003
Cost of Nonadherence: Adjusted all cause:

Outpatient state specific costs

Pharmacy costs

Physician office visit costs

Pharmacy costs

Medical costs

Short term costs

Type of Costs: adjusted and unadjusted classification:
all cause and disease state specific
Currency Year: USD, 2003
Cost of Nonadherence: Adjusted all cause:

Quality: medium
Classification: cost description
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Total Healthcare Costs</th>
<th>Type of Costs</th>
<th>Classification</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen et al [31]</td>
<td>2010</td>
<td>US</td>
<td>To compare all cause total health care costs and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.</td>
<td>Retrospective, cohort study</td>
<td>2 years</td>
<td>A:63830, NA:44762</td>
<td>MPR</td>
<td>MPR≥80% = adherent, MPR&lt;80% = nonadherent</td>
<td>PC: $1668 ($2065.99), Adjusted disease state specific: HC: $7642 ($9465.39), PC: $614 ($760.50), MC: $5974 ($7399.40), STDC: $1840 ($2279.03)</td>
<td>Adjusted and unadjusted</td>
<td>all cause and disease state specific</td>
<td>USD, 2005</td>
<td>Adjusted all cause: THC: $13258 ($15911.01)</td>
<td>medium</td>
<td>cost description</td>
</tr>
<tr>
<td>Hong et al [32]</td>
<td>2011</td>
<td>South Korea</td>
<td>To assess the relationship between initial adherence to oral antihyperglycemic medications and</td>
<td>Retrospective, cohort study</td>
<td>3 years</td>
<td>A:11800, NA:28282</td>
<td>MPR</td>
<td>MPR≥80% = adherent, MPR&lt;80% = nonadherent</td>
<td>PC: $1727 ($2139.06), Adjusted disease state specific: HC: $6919 ($8569.88), PC: $785 ($972.30), MC: $5192 ($6430.82), STDC: $1717 ($2126.68)</td>
<td>Unadjusted</td>
<td>all cause and disease state specific</td>
<td>KRW, 2007</td>
<td>THC: $765483 ($1142.31)</td>
<td>medium</td>
<td>cost description</td>
</tr>
<tr>
<td>Jha et al[33]</td>
<td>2012</td>
<td>US</td>
<td>How often do previously non-adherent patients become adherent and vice versa?</td>
<td>Design: Retrospective, observational claims analysis</td>
<td>Measure: MPR</td>
<td>Total costs</td>
<td>Type of Costs: adjusted</td>
<td>Quality: high</td>
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<td>Classification: MPR ≥ 80% = adherent, MPR &lt; 80% = nonadherent</td>
<td>ED costs</td>
<td>Classification: disease state specific</td>
<td>Classification: cost outcome description</td>
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<td>Hospitalization costs</td>
<td>Currency Year: USD, 2011</td>
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<tr>
<td>White et al[34]</td>
<td>2004</td>
<td>US</td>
<td>To assess the relationship between diabetic medication adherence, total</td>
<td>Design: Retrospective, database analysis</td>
<td>Measure: MPR</td>
<td>Total costs</td>
<td>Type of Costs: adjusted and unadjusted</td>
<td>Quality: low</td>
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<td>Classification: MPR ≥ 95%, MPR &gt; 75% &lt; 95%</td>
<td>Pharmacy costs</td>
<td>Classification: disease state specific</td>
<td>Classification: cost analysis</td>
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<td>Non-pharmacy costs</td>
<td>Currency Year: USD, 2000</td>
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<td>Cost of Nonadherence: adjusted:</td>
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<td></td>
<td>TC:$4680000000 ($5006563305.49), EDC:$735000000 ($786287185.80), HC:$3950000000 ($4225625012.11)</td>
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healthcare costs and utilisation with patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease.

MPR<75% costs

TC(≥95): $4835 ($6518.17),
TC(75-95): $5314 ($7163.92),
TC(<75): $5706 ($7692.38),
PC(≥95): $1429 ($1926.47),
PC(75-95): $1157 ($1559.78),
PC(<75): $762 ($1027.27),
NPC(≥95): $3406 ($4591.70),
NPC(75-95): $4157 ($5604.14),
NPC(<75): $4944 ($6665.11)

Unadjusted:

TC(≥95): $4809 ($6483.12),
TC(75-95): $5333 ($7189.53),
TC(<75): $5605 ($7556.22),
PC(≥95): $1402 ($1890.07),
PC(75-95): $1153 ($1554.38),
PC(<75): $766 ($1032.66),
NPC(≥95): $3407 ($4593.05),
NPC(75-95): $4180 ($5635.15),
NPC(<75): $4839 ($6523.56)

Wu et al[35] 2009 US

To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

Design: Retrospective, cohort study
Follow Up: 1 year
Sample Size: 2354 (A:830, NA:1524)

Measure: MPR
Classification: MPR≥80%= high compliance,
MPR<80% = low compliance

Subgroup Analysis: commercial and Medicare supplemental

Method of Assessment: pharmacy claims
data

Total healthcare costs
Inpatient costs
Outpatient costs
Pharmacy costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2006
Cost of Nonadherence: adjusted all cause:

THC(com): $32407 ($37732.29),
THC(med): $24622 ($28668.02),
IC(com): $2851 ($14692.74),
IC(med): $754 ($7863.85),
OC(com): $1888 ($13841.50),
OC(med): $10598 ($12339.52),
PC(com): $1667 ($8926.88),
PC(med): $270 ($8464.65)

Quality: medium
Classification: cost description
Osteoporosis

Briesacher et al.[36] 2007 US

To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.

**Design:** Retrospective, cohort study

**Follow Up:** 3 years

**Sample Size:** 17988 (not specified)

**Measure:** MPR

**Classification:** disease state specific

**Quality:** medium

**Method of Total costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>adjusted and unadjusted</th>
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</thead>
<tbody>
<tr>
<td>Classification</td>
<td>disease state specific</td>
</tr>
<tr>
<td>Currency Year</td>
<td>USD, 2004</td>
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</table>

**Cost of Nonadherence****:

<table>
<thead>
<tr>
<th>Classification</th>
<th>adjusted costs</th>
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<tbody>
<tr>
<td>IC(80-100)</td>
<td>$2653 (-$3072.33)</td>
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<tr>
<td>IC(60-79)</td>
<td>$3956 (-$4403.30)</td>
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<td>IC(40-59)</td>
<td>$5622 ($7705.34)</td>
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<td>IC(20-39)</td>
<td>$658 (-$724.58)</td>
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<tr>
<td>TC(80-100)</td>
<td>$10024 ($11671.20)</td>
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<td>TC(60-79)</td>
<td>$5015 ($5839.09)</td>
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<td>TC(40-59)</td>
<td>$2232 ($2598.77)</td>
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<td>TC(20-39)</td>
<td>$1451 ($1689.44)</td>
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<tr>
<td>OC(80-100)</td>
<td>$3565 ($4150.82)</td>
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<td>OC(60-79)</td>
<td>$2384 ($2775.75)</td>
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<td>OC(40-59)</td>
<td>$1739 ($2024.76)</td>
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<tr>
<td>OC(20-39)</td>
<td>$1464 ($1704.57)</td>
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<tr>
<td>PC(80-100)</td>
<td>$2231 ($2496.28)</td>
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<td>PC(60-79)</td>
<td>$181 ($210.74)</td>
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<td>PC(40-59)</td>
<td>$179 ($1372.74)</td>
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<td>PC(20-39)</td>
<td>$1179 ($1372.74)</td>
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<td>IC(80-100)</td>
<td>$3232 ($3903.40)</td>
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<td>IC(60-79)</td>
<td>$856 ($1060.24)</td>
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<tr>
<td>IC(40-59)</td>
<td>$585 (-$724.58)</td>
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<tr>
<td>IC(20-39)</td>
<td>$445 (-$551.18)</td>
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**Cost of Nonadherence****:

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<tr>
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<th>adjusted costs</th>
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<tbody>
<tr>
<td>IC(80-100)</td>
<td>$1989 ($2315.84)</td>
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<tr>
<td>IC(60-79)</td>
<td>$1231 ($1433.28)</td>
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<tr>
<td>IC(40-59)</td>
<td>$1179 ($1372.74)</td>
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<td>IC(20-39)</td>
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<td>$1179 ($1372.74)</td>
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<tr>
<td>IC(20-39)</td>
<td>$1179 ($1372.74)</td>
</tr>
<tr>
<td>Eisenberg et al[37]</td>
<td>To determine healthcare outcomes associated with compliance and noncompliance to bisphosphonate therapy in women diagnosed with osteoporosis</td>
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<tr>
<td>2015 US</td>
<td>Follow Up: 2 years</td>
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</table>

Assessment: pharmacy claims data


To examine the associations of adherence to osteoporosis therapies with occurrence of closed fracture, all cause medical costs and all cause hospitalizations.

**Design:** Retrospective analysis  
**Follow Up:** 540 days  
**Sample Size:** 21655  
(≥80%:8759,  
≥50<80%:5237,  
<50%:7659)

**Measure:** MPR  
**Classification:** (≥80% = high adherence,  
≥50<80% = moderate adherence, <50% = low adherence)  
**Method of Assessment:** pharmacy claims data  
**Medical costs**  
**Type of Costs:** unadjusted  
**Classification:** all cause  
**Currency Year:** USD, 2006  
**Cost of Nonadherence:** commercial:  
MC(≥80):$4295 ($5000.78),  
MC(50-80):$4697 ($5468.84),  
MC(<50):$5596 ($6515.56)  
Medicare:  
MC(≥80):$4590 ($5344.25),  
MC(50-80):$5536 ($6445.71),  
MC(<50):$5801 ($6754.25)  

**Quality:** medium  
**Classification:** cost outcome description

To evaluate the healthcare utilisation patterns of medicare part D beneficiaries newly initiating teriparatide and to assess the association of medication adherence and persistence with bone fracture.

**Design:** Retrospective cohort study  
**Follow Up:** 12 months  
**Sample Size:** 761  
(≥80%:163,  
≥50<80%:57,  
<50%:541)

**Measure:** PDC  
**Classification:** (≥80% = high adherence,  
≥50<80% = moderate adherence, <50% = low adherence)  
**Method of Assessment:** pharmacy claims data  
**Total healthcare costs**  
**Type of Costs:** unadjusted  
**Classification:** disease state specific and fracture related  
**Currency Year:** USD, 2010  
**Cost of Nonadherence:**  
Disease state specific:  
THC(≥80):$21033 ($22942.39),  
THC(50-80):$25574 ($27895.62),  
THC(<50):$15528 ($16937.64)  
IC(≥80):$2197 ($2292.24),  
IC(50-80):$25574 ($27895.62)  
IC(<50):$15528 ($16937.64)  

**Quality:** medium  
**Classification:** cost outcome description
<p>| Huybrechts et al[40] | To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice. | Design: Retrospective cohort study | Measure: MPR Classification: (≥80% = compliant, &lt;50% = noncompliant) Method of Assessment: pharmacy claims | Total costs | Medical costs | Institutional costs | Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2000 Cost of Nonadherence: | Quality: low Classification: cost description |
|---------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------|-----------|-----------------|--------------------------|-----------------------------|
| 2006 US             | Follow Up: 5 years Sample Size: 38120 (A:9530, NA:28590)                                                                 |                                   |                                                                                                 |           |                 |                          |                             |                         |
|                     |                                                                                                                |                                  |                                                                                                 |           |                 |                          |                             |                         |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Total Costs</th>
<th>Fracture Costs</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Kjellberg <em>et al</em> [41]</td>
<td>2016</td>
<td>Denmark</td>
<td>To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of noncompliance with health care resource use and cost.</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>38234 (A:26806, NA:11428)</td>
<td>MPR</td>
<td>(≥70% = compliant, &lt;70% = noncompliant)</td>
<td>Pharmacy claims data</td>
<td>Medical costs</td>
<td>Type of Costs: adjusted</td>
<td>Quality: high</td>
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<td>Classification: all cause and disease state specific</td>
<td>Classification: cost outcome description</td>
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<td>Disease costs: TC: €3471 (€4369.20), MC: €246 (€304.80), Disease state specific: TC: €426 (€536.24), MC: €246 (€304.80)</td>
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<td>All cause costs: TC: €4933 (€6209.58), MC: €426 (€536.24), Disease state specific: TC: €754 (€949.12), MC: €426 (€536.24)</td>
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<td>Cost of Nonadherence: all cause: TC: €4933 (€6209.58), MC: €3471 (€4369.20), Disease state specific: TC: €754 (€949.12), MC: €426 (€536.24)</td>
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<tr>
<td>Modi <em>et al</em> [42]</td>
<td>2015</td>
<td>US</td>
<td>To evaluate compliance with osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>27913 (A:23430, NA:34483)</td>
<td>MPR</td>
<td>(≥80% = compliant, &lt;80% = noncompliant)</td>
<td>Healthcare claims data</td>
<td>Medical costs</td>
<td>Type of Costs: unadjusted</td>
<td>Quality: medium</td>
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<td>Classification: all cause and disease state specific</td>
<td>Classification: cost outcome description</td>
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<td>Currency Year: USD, 2011</td>
<td>Cost of Nonadherence: all cause: TC: $11749 ($12484.12), IC: $8768 ($9316.60), OC: $3945 ($4191.83), EDC: $104 ($110.51), PC: $2981 ($3167.52), MC: $8768 ($9316.60), OtC: $997 ($1059.38)</td>
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<td>Disease state specific: TC: $630 ($694.42), IC: $443 ($470.72), OC: $158 ($167.89), EDC: $3 ($3.19), PC: $325 ($345.33), OtC: $26 ($27.63)</td>
<td></td>
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<tr>
<td>Olsen <em>et al</em> [43]</td>
<td>2013</td>
<td>Denmark</td>
<td>To assess the association between refill compliance and fracture costs</td>
<td>Retrospective observational study</td>
<td>2 years</td>
<td>28,000 (A:20,000, NA:8000)</td>
<td>MPR</td>
<td>(≥80% = optimal)</td>
<td>Pharmacy claims data</td>
<td>Fracture costs</td>
<td>Type of Costs: unadjusted</td>
<td>Quality: medium</td>
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<td>Classification: fracture site specific</td>
<td>Classification: cost analysis</td>
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</table>
all cause health care costs.

Sample Size: 47176 (not specified)

compliance,
>50<80% = suboptimal compliance,
<50% = low compliance

Method of Assessment: pharmacy claims data

Cost of Nonadherence:

Hip fracture:
FC(50-80): kr 817575.50 ($74531.41),
FC(<50): kr 454954 ($549987.04)

Spine fracture:
FC(50-80): kr 174700 ($21568.12),
FC(<50): kr 26472 ($27959.14)

Humerus fracture:
FC(50-80): kr 117776.50 ($14540.12),
FC(<50): kr 5217.50 ($98173.70)

Forearm fracture:
FC(50-80): kr 463024 ($57162.70),
FC(<50): kr 45072.50 ($8665.81)

Other fracture:
FC(50-80): kr 19261.50 ($2377.93),
FC(<50): kr 684067.50 ($84451.66)

Sunycz et al[44] 2008

US

To examine the relationship between persistence and compliance with bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naive users.

Design: Retrospective observational study
Follow Up: 3 years
Sample Size: 32944 (A:12186, NA:20758)

Measure: MPR
Classification: (≥80% = compliant, <80% = noncompliant)
Method of Assessment: pharmacy claims data

Total healthcare costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Radiology costs

Cost of Nonadherence:

All cause:
THC: $23660 ($28394.52),
IC: $18839 ($22608.81),
OC: $10061 ($12074.27),
EDC: $832 ($988.45),
PC: $6941 ($8329.94),
RC: $1079 ($1294.91)

Disease state specific:
THC: $16026 ($1922.57),
IC: $14074 ($16890.30),
OC: $501 ($601.25),
EDC: $452 ($542.45),
Zhao et al[45]  
2014  
US  

To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.

**Design:** Retrospective cohort study  
**Follow Up:** 36 months  
**Sample Size:** 824  
(≥80:362, 50-80%:219, <50%:243)

**Measure:** PDC  
**Classification:** (≥80% = high, 50-80% = medium, <50% = low)

**Method of Assessment:** pharmacy claims data

**Total healthcare costs**  
Inpatient costs  
Outpatient costs  
Pharmacy costs

**Type of Costs:** adjusted and unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2010

**Cost of Nonadherence**:  
Adjusted:  
THC(≥80): $34428 ($37553.4),  
THC(50-80%): $37956 ($41401.68),  
THC(<50%): $31188 ($34019.28),  
IC(≥80): $72548 ($8233.20),  
IC(50-80%): $11520 ($12605.04),  
IC(<50%): $11556 ($12605.04),  
OC(≥80): $9312 ($10157.40),  
OC(50-80%): $12816 ($13979.40),  
OC(<50%): $13044 ($14228.16),  
PC(≥80): $18864 ($20576.52),  
PC(50-80%): $13116 ($14306.64),  
PC(<50%): $7452 ($8128.44)

Unadjusted:  
THC(≥80): $37464 ($40865.04),  
THC(50-80%): $35076 ($38260.20),  
THC(<50%): $29484 ($32160.60),  
IC(≥80): $7512 ($7735.80),  
IC(50-80%): $11100 ($12107.64),  
IC(<50%): $11532 ($12516.17),  
OC(≥80): $9900 ($10798.68),  
OC(50-80%): $11352 ($12382.56),  
OC(<50%): $13908 ($14968.28),  
PC(≥80): $20484 ($22343.52),  
PC(50-80%): $12624 ($13770),  
PC(<50%): $6864 ($7487.16)

**Quality:** medium
association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients.

**Design:** Observational cohort study

**Follow Up:** 36 months

**Sample Size:** 1568

(≥80%: 783, 50-80%: 382, <50%: 403)

**Method of Assessment:** Pharmacy claims data

**Classification:** (≥80% = high, 50-80% = medium, <50% = low)

**Classification:** Healthcare costs

Inpatient costs

Outpatient costs

Pharmacy costs

**Classification:** Disease state specific

**Currency Year:** USD, 2010

**Cost of Nonadherence:**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Classification</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC(≥80)</td>
<td>$42768 ($46650.48)</td>
<td>$42012 ($43862.52)</td>
<td></td>
</tr>
<tr>
<td>THC(50-80)</td>
<td>$36780 ($40118.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC(&lt;50)</td>
<td>$39792 ($43404.36)</td>
<td></td>
<td></td>
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<tr>
<td>IC(≥80)</td>
<td>$7620 ($8311.80)</td>
<td></td>
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<tr>
<td>IC(50-80)</td>
<td>$12228 ($13338.12)</td>
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<td>$15768 ($17199.48)</td>
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</tr>
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<tr>
<td>PC(&lt;50)</td>
<td>$8700 ($9843.24)</td>
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</tr>
</tbody>
</table>

Respiratory Disease

**Design:** Retrospective longitudinal cohort

**Measure:** MPR

**Total costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Classification</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
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<td>THC(≥80)</td>
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</table>
### US adherence with fluticasone propionate/salmeterol combination product in a single inhaler and asthma care utilisation and costs in asthma patients in typical US clinical practice

**Study**
- **Follow Up:** 24 months
- **Sample Size:** 12907
  - (≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)

**Method of Assessment:** pharmacy claims data

<table>
<thead>
<tr>
<th>Category</th>
<th>≥75</th>
<th>50-75</th>
<th>25-50%</th>
<th>&lt;25%</th>
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</thead>
<tbody>
<tr>
<td>TC</td>
<td>$1564</td>
<td>$1128</td>
<td>$900</td>
<td>$632</td>
</tr>
<tr>
<td>OC</td>
<td>$1272</td>
<td>$852</td>
<td>$600</td>
<td>$388</td>
</tr>
<tr>
<td>EDC</td>
<td>$32</td>
<td>$36</td>
<td>$60</td>
<td>$48</td>
</tr>
<tr>
<td>OtC</td>
<td>$292</td>
<td>$276</td>
<td>$300</td>
<td>$240</td>
</tr>
</tbody>
</table>

**Currency Year:** USD, 2003

**Follow Up:** 24 months

**Sample Size:** 12907
- (≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)

**Method of Assessment:** pharmacy claims data

<table>
<thead>
<tr>
<th>Category</th>
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<th>50-75</th>
<th>25-50%</th>
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<tr>
<td>OtC</td>
<td>$292</td>
<td>$276</td>
<td>$300</td>
<td>$240</td>
</tr>
</tbody>
</table>

**Design:** Retrospective claims analysis
**Measure:** 37 day gap in claims
**Classification:** (>37 day gap in claims = noncompliant)
**Method of Assessment:** pharmacy claims data

**Cost of Nonadherence:**
- TC(≥75): $1564 ($1990.27),
- TC(50-75): $1128 ($1435.44),
- TC(25-50): $900 ($1145.30),
- TC(<25): $632 ($804.25),
- OC(≥75): $1272 ($1618.69),
- OC(50-75): $852 ($1084.21),
- OC(25-50): $600 ($763.53),
- OC(<25): $388 ($493.75),
- EDC(≥75): $32 ($40.72),
- EDC(50-75): $36 ($45.81),
- EDC(25-50): $60 ($76.35),
- EDC(<25): $48 ($61.08),
- OtC(≥75): $292 ($371.59),
- OtC(50-75): $276 ($351.22),
- OtC(25-50): $300 ($381.77),
- OtC(<25): $240 ($305.41)

**Quality:** medium

---

**Diehl et al.[48] 2010**

To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and received palivizumab in accordance with the dosing schedule recommended by the American Academy of Paediatrics in 2006 versus those who did not.

**Design:** Retrospective claims analysis
**Follow Up:** 7 months
**Sample Size:** 245 (A:73, NA:172)

**Measure:** 37 day gap in claims
**Classification:** (>37 day gap in claims = noncompliant)
**Method of Assessment:** pharmacy claims data

**Cost of Nonadherence:**
- TC: $19093.46 ($21656.12),
- PC: $7647.40 ($8673.81),
- SC**: $11604.03 ($13161.45)

**Quality:** medium

---

**Joshi et al.[49] 2006**

Examine the association of...

**Design:** quantitative analysis
**Measure:** Morisky scale
**Total productivity**

**Cost of Nonadherence:**
- TC: $19093.46 ($21656.12),
- PC: $7647.40 ($8673.81),
- SC**: $11604.03 ($13161.45)

**Quality:** medium
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
<th>Outcome Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).</td>
<td>To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).</td>
<td>Multicentre, retrospective, observational study</td>
<td>18 months</td>
<td>1365 (A:246, NA:1119)</td>
<td>GOLD 2007 Guidelines</td>
<td>(adherent, nonadherent)</td>
<td>Unadjusted</td>
<td>EUR, 2009</td>
<td>TPC(0): €40.83 ($57.91), TPC(1-2): €771.50 ($1094.27), TPC(&gt;2): €106.29 ($150.76), PO: €101.61 ($144.12), POC: €123.84 ($175.65), IntC: €321.84 ($455.92), MTC: €36.66 ($51.99), RC: €24.24 ($34.38), LC: €17.35 ($24.61)</td>
<td>Medium</td>
<td>Disease state specific</td>
<td>Description</td>
</tr>
<tr>
<td>Miravitlles et al [50] 2013 Spain</td>
<td></td>
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<tr>
<td>Quittner et al [51] 2014 US</td>
<td>To evaluate associations of adherence to</td>
<td></td>
<td>Retrospective, cohort study</td>
<td>2 years</td>
<td></td>
<td>MPR</td>
<td>(≥80% = high)</td>
<td>Unadjusted</td>
<td>USD, 2002</td>
<td>TPC(0): $1210.90 ($1571.73), TPC(1-2): $1428.50 ($1854.17), TPC(&gt;2): $1073.10 ($1392.87), AbC(0): $633.70 ($822.53), AbC(1-2): $608.90 ($790.34), AbC(&gt;2): $474.80 ($616.28), PrC(0): $577.20 ($749.20), PrC(1-2): $819.60 ($1063.83), PrC(&gt;2): $598.30 ($776.59)</td>
<td>Medium</td>
<td>All cause and disease state specific</td>
<td>Description</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
<td>Hospitalization costs</td>
<td>Type of Costs</td>
<td>Classification</td>
<td>Currency Year</td>
<td>Cost of Nonadherence</td>
<td>Quality</td>
<td>Classification</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Pulmonary Medications, Age, Healthcare Use and Cost Among Cystic Fibrosis Patients</td>
<td>To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.</td>
<td>Retrospective, observational cohort claims analysis</td>
<td>12 months</td>
<td>3287 (≥80%: 663, 50-80%: 949, &lt;50%: 1675)</td>
<td>Number of infusions in 12 month period</td>
<td>Medium</td>
<td>Unadjusted</td>
<td>Disease state specific</td>
<td>USD, 2011</td>
<td>THC(≥80%): $35749.50 ($38244.05), THC(50-80%): $45031.50 ($48173.73), THC(&lt;50%): $50284.50 ($53793.28)</td>
<td>Medium</td>
<td>Cost description</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disease</td>
<td>Carter et al[52]</td>
<td>2011</td>
<td>US</td>
<td>To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.</td>
<td>Retrospective, observational cohort claims analysis</td>
<td>12 months</td>
<td>638 (A:466, NA:172)</td>
<td>Number of infusions in 12 month period</td>
<td>Medium</td>
<td>Disease state specific</td>
<td>USD, 2007</td>
<td>THC(≥80%): $23764 ($25422.22), THC(50-80%): $33132.50 ($35444.44), THC(&lt;50%): $33894 ($36259.07)</td>
<td>Medium</td>
</tr>
<tr>
<td>Gastrointestinal Disease</td>
<td>Gosselin et al[53]</td>
<td>2009</td>
<td>US</td>
<td>To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.</td>
<td>Retrospective cohort study</td>
<td>12 months</td>
<td>41837 (A:28321, NA:13516)</td>
<td>MPR</td>
<td>Medium</td>
<td>Disease state specific</td>
<td>USD, 2003</td>
<td>TC:$9497 ($12085.43), IC:$2116 ($2692.72), OC:$5458 ($6945.59), PC:$1922 ($2445.85), MC:$7575 ($9639.58)</td>
<td>Medium</td>
</tr>
</tbody>
</table>
To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by patients.

**Design:** retrospective cohort analysis

**Follow Up:** 12 months

**Sample Size:** 571 (A:375, NA:196)

**Measure:** number of infusions in 12 month period

**Classification:** (≥8 infusions = adherent, <7 infusions = nonadherent)

**Method of Assessment:** health claims data

**Type of Costs:** unadjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2004

**Cost of Nonadherence:**

- **OC:** $6679 ($8272.62),
- **EDC:** $314 ($388.92),
- **MC:** $16129 ($19977.40),
- **HC:** $6893 ($8537.68)

**Quality:** medium

**Classification:** cost outcome description

---

To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.

**Design:** retrospective, observational cohort study

**Follow Up:** 12 months

**Sample Size:** 1693 (A:476, NA:1216)

**Measure:** MPR

**Classification:** (≥80% = adherent, <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2010

**Cost of Nonadherence:**

- **PC:** $1541.60 ($1681.55)
- **Di state specific:**
  - **IC:** $28726.65 ($31334.47),
  - **OC:** $1145.67 ($1249.67),
  - **EDC:** $635.35 ($693.68),
  - **AC:** $4923.39 ($5370.23),
  - **NPC:** $14226.32 ($15517.79)

**Quality:** high

**Classification:** cost description

---

To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.

**Design:** retrospective cohort analysis

**Follow Up:** 360 days

**Sample Size:** 1646

**Measure:** MPR

**Classification:** (≥80% = adherent, <80% = nonadherent)

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2009

**Quality:** high

**Classification:** cost description
patients with inflammatory bowel disease.

Method of Assessment:
pharmacy claims data

Inpatient costs
Outpatient costs
ED costs
Pharmacy costs

Cost of Nonadherence:
All cause:
TC:$47411 ($52341.27),
THC:$32522 ($35903.96),
IC:$17634 ($19467.76),
OC:$10909 ($12043.43),
EDC:$458 ($505.63),
PC:$18410 ($20324.46)

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2003

Epilepsy

To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 10892
(A:6644, NA:4248)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment:
pharmacy claims data

Total costs
Inpatient costs
ED costs
Pharmacy costs
Other pharmacy costs

Cost of Nonadherence:
All cause:
TC:$1466 ($1865.56),
THC:$2714 ($3453.71),
IC:$526 ($669.36),
EDC:$358 ($455.57)

Type of Costs: unadjusted
Classification: cost description
Quality: medium

To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the

Design: retrospective claims analysis
Follow Up: 12 months
Sample Size: 1278
(A:758, NA:520)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)
Method of Assessment:
pharmacy claims data

Total costs
Inpatient costs
ED costs
Pharmacy costs
Other pharmacy costs
Physician Office visit

Cost of Nonadherence:
All cause:
TC:$17817 ($22673.06),
THC:$32652 ($37151.47),
IC:$18764 ($20715.27),
OC:$12564 ($13870.53),
EDC:$48 ($52.99),
PC:$15150 ($16725.45)

Type of Costs: unadjusted
Classification: cost description
Quality: medium

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.

**Faught et al [59] 2009 US** To study the impact of non-adherence to antiepileptic drugs (AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.

- **Design:** retrospective observational open cohort design
- **Follow Up:** 4.65 years
- **Sample Size:** 33658 (A:24907, NA:8751)
- **Measure:** MPR
- **Classification:** (≥80% = adherent, <80% = nonadherent)
- **Method of Assessment:** pharmacy claims data
- **Type of Costs:** unadjusted

**Ancillary costs**
- PC:$347 ($441.58),
- POC:$3063 ($3897.83),
- AC:$8344 ($10618.18),
- Other pharmacy costs OtPC:$2822 ($3591.14)

**Quality:** medium

**HIV/AIDS**


- **Design:** retrospective observational cohort study
- **Follow Up:** 1 year
- **Sample Size:** 1896 (not specified)
- **Measure:** antiretroviral taking behaviour
- **Classification:** (85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent)
- **Method of Assessment:** pharmacy claims data
- **Currency Year:** USD, 2006
- **Cost of Nonadherence**
  - High viral load:
    - TC:$25824 ($30067.54)
    - Low viral load:
      - TC:$20509.67 ($23879.92)

**Quality:** medium

**Cooke et al [61]** To measure adherence

- **Design:** retrospective
- **Measure:** MPR
- **Total**
- **Type of Costs:** unadjusted

**Quality:** medium
### 2014 US

to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors associated with ≥90% adherence.

**Follow Up:** 1 year

**Sample Size:** 3528 (A:1737, NA:640)

**Method of Assessment:** pharmacy claims data

**Classification:**
- ≥90% = adherent,
- <90% = nonadherent

**Type of Costs:** unadjusted

**Currency Year:** USD, 2011

**Cost of Nonadherence:**
- THC:$18868 ($20184.58),
- IC:$2700 ($2888.40),
- OC:$915 ($978.85),
- PC:$15253 ($16317.33)

---

### Pruitt et al[62] 2015 US

To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.

**Design:** retrospective cohort study

**Follow Up:** 2 years

**Sample Size:** 502 (A:56, NA:176)

**Method of Assessment:** pharmacy claims data

**Classification:**
- ≥90% = adherent,
- <90% = nonadherent

**Type of Costs:** unadjusted

**Currency Year:** USD, 2009

**Cost of Nonadherence:**
- HIV:
  - TC:$15360 ($16957.32),
  - IC:$3864 ($4265.76),
  - OC:$3948 ($4358.52),
  - PC:$4956 ($5471.40),
  - OtPC:$1764 ($1947.48),
  - BHIC:$840 ($927.36)
- AIDS:
  - TC:$27648 ($30523.08),
  - IC:$13008 ($14360.76),
  - OC:$5880 ($6491.52),
  - PC:$5640 ($6226.56),
  - OtPC:$2580 ($2848.32),
  - BHIC:$5283 ($582.96)

---

### Parkinson’s Disease

**Davis et al[63] 2010 US**

To assess the extent to which patients diagnosed with Parkinson’s disease are

**Design:** retrospective administrative claims study

**Follow Up:** 12 months

**Measure:** MPR

**Classification:**
- ≥80% = adherent,
- <80% = nonadherent

**Type of Costs:** unadjusted

**Currency Year:** USD, 2001

**Cost of Nonadherence:**
- TC:$27648 ($30523.08),
- IC:$13008 ($14360.76),
- OC:$5880 ($6491.52),
- PC:$5640 ($6226.56),
- OtPC:$2580 ($2848.32),
- BHIC:$5283 ($582.96)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delea et al [64]</td>
<td>2011</td>
<td>Retrospective historical cohort study</td>
<td>3119 (A:1211, NA:1908)</td>
<td>PDC</td>
<td>TC: $18511 ($24262.36), PC: $2684 ($3537.36), MC: $1582 ($20859.12)</td>
<td>Adjusted and unadjusted</td>
<td>High</td>
</tr>
<tr>
<td>Wei et al [65]</td>
<td>2014</td>
<td>Retrospective cross-sectional study</td>
<td>1215 (A:617, NA:598)</td>
<td>MPR</td>
<td>TC: $19686 ($23625.30), IC: $5954 ($7145.43), PC: $6391 ($7669.88), Otc: $8795 ($10554.94)</td>
<td>Unadjusted</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Notes:
- TC: Total costs
- IC: Inpatient costs
- PC: Pharmacy costs
- Otc: Other costs
- Design: retrospective historical cohort study
- Measure: PDC (≥80% = satisfactory, <80% = unsatisfactory)
- Classification: all cause and disease state specific
- Currency Year: USD, 2005

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
### US Adherence to Antiparkinson Drugs

**Follow Up:** 19 months  
**Sample Size:** 7583 (90-100%: 3948, 80-89%: 1456, ≤79%: 2179)

(>90<100% = high, >80<89% = moderate, ≤79% = low)  
**Method of Assessment:** pharmacy claims data  

<table>
<thead>
<tr>
<th>Cost of Nonadherence</th>
<th>TC(90-100%)</th>
<th>TC(80-89%)</th>
<th>TC(≤79%)</th>
<th>IC(90-100%)</th>
<th>IC(80-89%)</th>
<th>IC(≤79%)</th>
<th>OC(90-100%)</th>
<th>OC(80-89%)</th>
<th>OC(≤79%)</th>
<th>PC(90-100%)</th>
<th>PC(80-89%)</th>
<th>PC(≤79%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USD, 2007</td>
<td>$36407 ($41293.43)</td>
<td>$43417 ($49244.29)</td>
<td>$45867 ($52023.13)</td>
<td>$15294 ($17346.71)</td>
<td>$21603 ($24502.49)</td>
<td>$24727 ($28045.78)</td>
<td>$10155 ($11517.97)</td>
<td>$11838 ($13426.86)</td>
<td>$12889 ($14618.92)</td>
<td>$10957 ($12427.61)</td>
<td>$9976 ($11314.95)</td>
<td>$8251 ($9358.42)</td>
</tr>
</tbody>
</table>

### Musculoskeletal

Ivanova et al. [66]  
2012  
US

To compare the rates of severe relapse and total direct and indirect costs over a 2 year period between US based employees with MS who were adherent and non-adherent to disease modifying drugs.

**Design:** retrospective cohort study  
**Follow Up:** 2 years  
**Sample Size:** 648 (A: 448, NA: 200)

**Measure:** MPR  
**Classification:** (≥80% = adherent, <80% = nonadherent)  
**Method of Assessment:** pharmacy claims data

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Total costs</th>
<th>Total healthcare costs</th>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
<th>ED costs</th>
<th>Pharmacy costs</th>
<th>Medical costs</th>
<th>Short term disability costs</th>
<th>Absenteeism cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause:</td>
<td>TC: $8079 ($9276.76), THC: $6027 ($6830.25), IC: $1030.50 ($1168.81), OC: $3231 ($3664.65), PC: $1617 ($1834.03), MC: $4405 ($4996.79)</td>
<td>TC: $3005 ($3408.32), IC: $505 ($572.78), OC: $1710 ($1939.51), PC: $37 ($41.97)</td>
<td>ED: $143.50 ($162.76)</td>
<td>PC: $1617 ($1834.03)</td>
<td>MC: $4405 ($4996.79)</td>
<td>TC: $3005 ($3408.32), IC: $505 ($572.78), OC: $1710 ($1939.51), PC: $37 ($41.97)</td>
<td>TC: $3005 ($3408.32), IC: $505 ($572.78), OC: $1710 ($1939.51), PC: $37 ($41.97)</td>
<td>TC: $3005 ($3408.32), IC: $505 ($572.78), OC: $1710 ($1939.51), PC: $37 ($41.97)</td>
<td>TC: $3005 ($3408.32), IC: $505 ($572.78), OC: $1710 ($1939.51), PC: $37 ($41.97)</td>
</tr>
</tbody>
</table>

**Currency Year:** USD, 2007  
**Cost of Nonadherence:**

Quality: high  
Classification: cost outcome description
Tan et al[67]
2011
US
To assess the impact of treatment adherence on MS related hospitalizations (inpatient), ER visits, MS relapses and medical costs.

Design: retrospective cohort study
Follow Up: 12 months
Sample Size: 2446 (A:1459, NA:987)

Measure: MPR
Classification:
≥80% = adherent, <80% = nonadherent

Method of Assessment:
pharmacy claims data

Medical costs
Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence:
Adjusted: MC:$4348 ($5062.49)
Unadjusted: MC:$5179 ($6030.04)

Quality: medium
Classification: cost description

Zhao et al[68]
2011
US
To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.

Design: retrospective cohort analysis
Follow Up: 12 months
Sample Size: 5435 (A:1744, NA:3691)

Measure: MPR
Classification:
≥80% = adherent, <80% = nonadherent

Method of Assessment:
pharmacy claims data

Total costs
Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
Commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40)
Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)

Quality: medium
Classification: cost analysis

Cancer
Darkow et al[69]
2007
US
Estimate the association between treatment interruptions and non-adherence with

Design: retrospective observational cohort analysis
Follow Up: 12 months
Sample Size: 267

Measure: MPR
Classification:
≥95% = very high, >90<95% = high, >50<90% =

Total healthcare costs
Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2004
Cost of Nonadherence:
THC(≥95):$42250 ($52330.90),
imatinib and healthcare costs for US managed care patients. Intermediate, <50% = low)

**Method of Assessment:** pharmacy claims data

**Design:** retrospective

**Measure:** MPR

**Quality:** medium

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>THC(≥95%%)</th>
<th>THC(90-95%%)</th>
<th>THC(&lt;90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$39236</td>
<td>$54770</td>
<td>$31357</td>
</tr>
<tr>
<td>Low</td>
<td>$1362</td>
<td>$19096</td>
<td>$9096</td>
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<tr>
<td>Other pharmacy costs</td>
<td>$1362</td>
<td>$19096</td>
<td>$9096</td>
</tr>
<tr>
<td>Other costs</td>
<td>$131357</td>
<td>$54770</td>
<td>$31357</td>
</tr>
<tr>
<td>THC(≥95%)</td>
<td>$48597.76</td>
<td>$67838.19</td>
<td>$162698.93</td>
</tr>
<tr>
<td>THC(90-95%)</td>
<td>$1431.82</td>
<td>$1686.97</td>
<td>$23652.33</td>
</tr>
<tr>
<td>THC(&lt;90%)</td>
<td>$101035.18</td>
<td>$23652.33</td>
<td>$162698.93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>IC(≥95%)</th>
<th>IC(90-95%)</th>
<th>IC(50-90%)</th>
<th>IC(&lt;50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$1156</td>
<td>$1362</td>
<td>$19096</td>
<td>$81572</td>
</tr>
<tr>
<td>Low</td>
<td>$1431.82</td>
<td>$1686.97</td>
<td>$23652.33</td>
<td>$101035.18</td>
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<tr>
<td>Other pharmacy costs</td>
<td>$1148</td>
<td>$14631</td>
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</tr>
<tr>
<td>Other costs</td>
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<td>$1362</td>
<td>$19096</td>
<td>$81572</td>
</tr>
<tr>
<td>IC(≥95%)</td>
<td>$1431.82</td>
<td>$1686.97</td>
<td>$23652.33</td>
<td>$101035.18</td>
</tr>
<tr>
<td>IC(90-95%)</td>
<td>$1686.97</td>
<td>$23652.33</td>
<td>$162698.93</td>
<td>$101035.18</td>
</tr>
<tr>
<td>IC(&lt;50%)</td>
<td>$23652.33</td>
<td>$162698.93</td>
<td>$101035.18</td>
<td>$101035.18</td>
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<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>OC(≥95%)</th>
<th>OC(90-95%)</th>
<th>OC(50-90%)</th>
<th>OC(&lt;50%)</th>
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</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$9299</td>
<td>$11148</td>
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<td>Low</td>
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<tr>
<td>Other pharmacy costs</td>
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<tr>
<td>Other costs</td>
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<td>$11148</td>
<td>$19096</td>
<td>$81572</td>
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<tr>
<td>OC(≥95%)</td>
<td>$1431.82</td>
<td>$1686.97</td>
<td>$23652.33</td>
<td>$101035.18</td>
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<td>OC(90-95%)</td>
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<td>$23652.33</td>
<td>$162698.93</td>
<td>$101035.18</td>
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<tr>
<td>OC(&lt;50%)</td>
<td>$23652.33</td>
<td>$162698.93</td>
<td>$101035.18</td>
<td>$101035.18</td>
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<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>EDC(≥95%)</th>
<th>EDC(90-95%)</th>
<th>EDC(50-90%)</th>
<th>EDC(&lt;50%)</th>
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</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$36</td>
<td>$568</td>
<td>$104</td>
<td>$183</td>
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<tr>
<td>Low</td>
<td>$44.59</td>
<td>$703.53</td>
<td>$128.81</td>
<td>$226.66</td>
</tr>
<tr>
<td>Other pharmacy costs</td>
<td>$2056</td>
<td>$23693</td>
<td>$18330</td>
<td>$104</td>
</tr>
<tr>
<td>Other costs</td>
<td>$36</td>
<td>$568</td>
<td>$104</td>
<td>$183</td>
</tr>
<tr>
<td>EDC(≥95%)</td>
<td>$44.59</td>
<td>$703.53</td>
<td>$128.81</td>
<td>$226.66</td>
</tr>
<tr>
<td>EDC(90-95%)</td>
<td>$703.53</td>
<td>$128.81</td>
<td>$226.66</td>
<td>$104</td>
</tr>
<tr>
<td>EDC(&lt;50%)</td>
<td>$104</td>
<td>$128.81</td>
<td>$226.66</td>
<td>$104</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>PC(≥95%)</th>
<th>PC(90-95%)</th>
<th>PC(50-90%)</th>
<th>PC(&lt;50%)</th>
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</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$29056</td>
<td>$23693</td>
<td>$18330</td>
<td>$8733</td>
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<tr>
<td>Low</td>
<td>$35988.80</td>
<td>$29346.18</td>
<td>$22703.56</td>
<td>$10816.70</td>
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<tr>
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<td>$23693</td>
<td>$18330</td>
<td>$8733</td>
</tr>
<tr>
<td>Other costs</td>
<td>$29056</td>
<td>$23693</td>
<td>$18330</td>
<td>$8733</td>
</tr>
<tr>
<td>PC(≥95%)</td>
<td>$35988.80</td>
<td>$29346.18</td>
<td>$22703.56</td>
<td>$10816.70</td>
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<tr>
<td>PC(90-95%)</td>
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<td>$22703.56</td>
<td>$10816.70</td>
<td>$8733</td>
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<tr>
<td>PC(&lt;50%)</td>
<td>$8733</td>
<td>$10816.70</td>
<td>$8733</td>
<td>$8733</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>MC(≥95%)</th>
<th>MC(90-95%)</th>
<th>MC(50-90%)</th>
<th>MC(&lt;50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$10731</td>
<td>$13452</td>
<td>$34202</td>
<td>$116892</td>
</tr>
<tr>
<td>Low</td>
<td>$13291.43</td>
<td>$16661.66</td>
<td>$42362.64</td>
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<td>Other pharmacy costs</td>
<td>$10731</td>
<td>$13452</td>
<td>$34202</td>
<td>$116892</td>
</tr>
<tr>
<td>Other costs</td>
<td>$10731</td>
<td>$13452</td>
<td>$34202</td>
<td>$116892</td>
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<tr>
<td>MC(≥95%)</td>
<td>$13291.43</td>
<td>$16661.66</td>
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<td>$144782.57</td>
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<td>$42362.64</td>
<td>$144782.57</td>
<td>$144782.57</td>
</tr>
<tr>
<td>MC(&lt;50%)</td>
<td>$42362.64</td>
<td>$144782.57</td>
<td>$144782.57</td>
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<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>OtPC(≥95%)</th>
<th>OtPC(90-95%)</th>
<th>OtPC(50-90%)</th>
<th>OtPC(&lt;50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>$2462</td>
<td>$20056</td>
<td>$23693</td>
<td>$5732</td>
</tr>
<tr>
<td>Low</td>
<td>$3049.44</td>
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<td>$2771.99</td>
<td>$7099.66</td>
</tr>
<tr>
<td>Other pharmacy costs</td>
<td>$2091</td>
<td>$2238</td>
<td>$5732</td>
<td>$241</td>
</tr>
<tr>
<td>Other costs</td>
<td>$2462</td>
<td>$20056</td>
<td>$23693</td>
<td>$5732</td>
</tr>
<tr>
<td>OtPC(≥95%)</td>
<td>$3049.44</td>
<td>$2589.92</td>
<td>$2771.99</td>
<td>$7099.66</td>
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<tr>
<td>OtPC(90-95%)</td>
<td>$2589.92</td>
<td>$2771.99</td>
<td>$7099.66</td>
<td>$241</td>
</tr>
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<td>OtPC(&lt;50%)</td>
<td>$7099.66</td>
<td>$2771.99</td>
<td>$7099.66</td>
<td>$241</td>
</tr>
</tbody>
</table>

**Wu et al[70]** To examine the

**Design:** retrospective  **Measure:** MPR  **Total costs**

**Type of Costs:** unadjusted  **Quality:** medium
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Country</th>
<th>Title</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Method of Assessment</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>US</td>
<td>For peer review only</td>
<td>2010 US association between adherence with imatinib and direct healthcare costs and resource utilisation</td>
<td>Observational cohort analysis</td>
<td>12 months</td>
<td>592 (A:350, NA:242)</td>
<td>Inpatient costs</td>
<td>Pharmacy claims data</td>
<td>≥85% = high adherence, &lt;85% = low adherence</td>
<td>Disease state specific</td>
<td>USD, 2008</td>
<td>Cost: TC: $107341 ($119415.73), IC: $4498 ($49503.55), OC: $34097 ($37932.55), EDC: $248 ($275.90), PC: $22846 ($25415.93), OtPC: $5652 ($6287.79)</td>
</tr>
<tr>
<td>2011</td>
<td>US</td>
<td>Addiction: Leider et al[71]</td>
<td>To assess the economic burden of chronic opioid users and to determine whether opioid regimen non-adherence contributes to increased healthcare costs.</td>
<td>Retrospective claims based analysis</td>
<td>12 months</td>
<td>2100 (A:442, NA:1658)</td>
<td>Total healthcare costs</td>
<td>Urine testing</td>
<td>Positive test = nonadherent, negative test = adherent</td>
<td>Disease state specific</td>
<td>USD, 2008</td>
<td>Cost: THC: $26433 ($29406.43), IC: $6361 ($7076.55), OC: $9734 ($10828.97), EDC: $421 ($468.36), PC: $7960 ($8855.42), MC: $1957 ($2177.14)</td>
</tr>
<tr>
<td>2014</td>
<td>US</td>
<td>Tkacz et al[72]</td>
<td>To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent members.</td>
<td>Retrospective cohort analysis</td>
<td>12 months</td>
<td>455 (A:146, NA:309)</td>
<td>Inpatient costs</td>
<td>Pharmacy claims data</td>
<td>≥80% = adherent, &lt;80% = nonadherent</td>
<td>Disease state specific</td>
<td>USD, 2010</td>
<td>Cost: THC: $49051 ($53503.88), IC: $26470 ($28872.96), OC: $14570 ($15892.67), EDC: $4498 ($4841.98), PC: $3581 ($3906.09), Unadjusted: THC: $4786 ($52213.49), IC: $26043 ($28407.20)</td>
</tr>
</tbody>
</table>
Metabolic conditions other than diabetes mellitus

Lee et al[73] 2011 US
To assess the relationship between medication adherence and healthcare costs among US patients on dialysis given cinacalcet to manage secondary hypoparathyroidism.

Design: retrospective cohort study
Follow Up: 12 months
Sample Size: 4923 (A:1372, NA:1304)

Measure: MPR
Classification: (≥80% = high adherent, <80% = low adherent)

Method of Assessment: pharmacy claims data

Total costs
Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010
Cost of Nonadherence:
All cause:
PC:$5556 ($6060.38)
Disease state specific:
TC:$ 126996 ($138524.78),
IC:$9780 ($10880.15),
OC:$101854 ($111100.37),
EDC:$734 ($800.63),
PC:$3244 ($3538.49),
OtPC:$9564 ($10432.23)

Quality: medium
Classification: cost description

Blood

Candrilli et al[74] 2011 US
To investigate the relationships among hydroxyurea adherence, healthcare utilisation and healthcare costs.

Design: retrospective longitudinal study
Follow Up: 12 months
Sample Size: 312 (A:110, NA:202)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Method of Assessment: pharmacy claims data

Total costs
Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
All cause:
TC: $ 20436 ($22734.83),
IC:$9780 ($10880.15),
ECD:$837 ($931.15),
PC:$2579 ($2869.11),
OtPC:$3483 ($3874.80),

Quality: medium
Classification: cost description
To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.

**Design:** retrospective observational study
**Follow Up:** 1527 days
**Sample Size:** 87 (A:21, NA:66)

<table>
<thead>
<tr>
<th>All</th>
<th>Alvarez Payero et al [75]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Spain</td>
<td>To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.</td>
</tr>
</tbody>
</table>

**Measure:** pharmacy records
**Classification:** (>75% = adherent, ≤75% = nonadherent)
**Method of Assessment:** pharmacy and hospital claims data

**Hospitalization costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
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<td><strong>Cost of Nonadherence</strong>:</td>
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<td><strong>All cause</strong>:</td>
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**Quality:** low
**Classification:** cost outcome description

*: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group; 
#: extrapolated annual cost and subgroups averaged; ###: cost represents losses in workplace productivity; ####: negative value as costs modelled against adherent group; #####: cost per episode of nonadherence
26. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003;11(12):817-22 doi: 10.2165/00115677-200311120-00006[published Online First: Epub Date]].

32. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;49:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]].


34. White TJV, Ann; Chang, Eunice; Dezii, Christopher M.; Abrams, Geoffrey D. The Costs of Non-Adherence to Oral Antihyperglycemic Medication in Individuals with Diabetes Mellitus and Concomitant Diabetes Mellitus and Cardiovascular Disease in a Managed Care Environment. Disease Management & Health Outcomes 2004;12(3):181-88 doi: 10.2165/00115677-200412030-00004[published Online First: Epub Date]].


43. Olsen KR, Hansen C, Abrahamsen B. Association between refill compliance to oral bisphosphonate treatment, incident fractures, and health care costs—an analysis using national health databases. Osteoporosis international : a journal established as result of cooperation between the European


# PRISMA 2009 Checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
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<th>Checklist item</th>
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<tbody>
<tr>
<td>TITLE</td>
<td></td>
<td><strong>Title</strong> 1 Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td>ABSTRACT</td>
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<td><strong>Structured summary</strong> 2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
</tr>
<tr>
<td>INTRODUCTION</td>
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<td><strong>Rationale</strong> 3 Describe the rationale for the review in the context of what is already known.</td>
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<td><strong>Objectives</strong> 4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<tr>
<td>METHODS</td>
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<td><strong>Protocol and registration</strong> 5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<td><strong>Eligibility criteria</strong> 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<td><strong>Information sources</strong> 7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<td><strong>Search</strong> 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<td><strong>Study selection</strong> 9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<td><strong>Data collection process</strong> 10 Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<td><strong>Data items</strong> 11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<td><strong>Risk of bias in individual studies</strong> 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<td><strong>Summary measures</strong> 13 State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<td><strong>Synthesis of results</strong> 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
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<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
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<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
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</table>

**RESULTS**

| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |

**DISCUSSION**

| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | |

**FUNDING**

| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |


For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).
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<tr>
<td><strong>Complete List of Authors</strong></td>
<td>Cutler, Rachelle; University of Technology, Sydney, Australia, Graduate School of Health; Pharmacy Fernandez-Llimos, Fernando; Universidade de Lisboa Instituto de Investigacao do Medicamento, Social Pharmacy Frommer, Michael; University of Sydney Sydney Medical School, Sydney Medical School Benrimoj, Charlie; University of Technology, Sydney, graduate school of health Garcia Cardenas, Victoria; University of Technology, Sydney, Australia, Graduate School of Health; Pharmacy</td>
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Title: Economic impact of medication nonadherence by disease groups: a systematic review

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+61 2 95147187

Word Count:

5967
Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in September 2017. Studies quantifying the cost of medication nonadherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy nine individual studies assessing the cost of medication nonadherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of nonadherence per person ranged from $949-$44,190 (in 2015 US dollars). Costs attributed to “all causes” nonadherence ranged from $5,271 to $52,341. Medication possession ratio was the metric most utilized to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338
Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication nonadherence via quantifying the cost of medication nonadherence across different disease groups.
- A large comprehensive review – 2,768 citations identified, 79 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.
1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources[2]. Medications represent a cost-effective treatment modality[3], but with estimates of 50% nonadherence to long term therapy for chronic illnesses[4], intentional and unintentional medication nonadherence signifies a prevalent and persistent healthcare problem. Medication adherence is defined as ‘the extent to which the patients’ behavior matches agreed recommendations from the prescriber’, emphasizing the importance on the patients’ decisions and highlighting the modifiable aspect of nonadherence[5].

Given the proportion of the population who do not adhere to their medication efforts to improve medication adherence represent an opportunity to enhance health outcomes and health system efficiency. Annual costings of medication nonadherence range from US$100-$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A$7 billion[8 9] in Australia. Additionally ten percent of hospitalizations in older adults are attributed to medication nonadherence [10 11] with the typical nonadherent patient requiring three extra medical visits per year leading to $2000 increased treatment costs per annum[12]. In diabetes the estimated costs savings associated with improving medication nonadherence range from $661 million to $1.16 billion [13]. Nonadherence is thus a critical clinical and economic problem[4].

Addressing the economic impact of medication nonadherence provides an opportunity for policy makers to help loosen the ever tightening constraints placed on health budgets. Healthcare reformers and payers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[14]. However there is still a budgetary problem that needs to be considered, especially given the widespread policy debate over how to best bend the healthcare cost curve downward[15] and the proportion of healthcare budgets spent on prescription medication[16]. Quantifying the cost of medication nonadherence will help demonstrate the causal effect between medication nonadherence, increased disease prevalence and healthcare resource use. Justification of the associated financial benefit may incentivize health policy discussion about the value of medication adherence and promote the adoption of medication adherence intervention programs [15].

The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the
literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.
2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[17].

2.1 Search strategy and selection criteria

A literature search was conducted in September 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB])) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence as a monetary value, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[18] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-
group analysis and statistical significance), conclusions and miscellaneous (funding source, references to other relevant studies, limitations and reviewers comments).

Costs were defined as any indicator associated with medication nonadherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients' families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [19], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [20]. All studies were classified in accordance with Drummond’s distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility
analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).

The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The
original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full
economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the
required item and zero if it did not with a maximum potential score of 28. The study was classified as
high quality if at least 75% of Drummond’s criteria were satisfied, medium quality if 51-74% were
satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

Outcome/indicator costs were independently extracted utilizing predesigned data extraction forms
(total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs,
emergency department costs, and hospitalisation costs) for the purpose of integrating the findings
on the cost of medication nonadherence to pool data and increase the power of analysis.
3 Results

3.1 Study Selection

Search strategies retrieved 2768 potential articles after duplicates were removed. Two hundred and eighty nine articles were selected for full text review. Seventy nine studies were included in the review (Figure 1). Numerous other papers do discuss nonadherence costs however addressed tangential issues or did not present primary relevant data. Many studies failed to report the monetary value of medication nonadherence associated with a range of cost estimate indicators.

3.2 Characteristics of individual studies

Sixty-six studies (83%) were conducted in the United States[10 22-86], four in Europe[87-90], four in Asia[91-94], three in Canada[95-97], one in the United Kingdom[98] and one across multiple countries throughout Europe and the United Kingdom[99]. Publication years ranged from 1997 to 2017, no date restriction filters were utilized with the earliest eligible study published in 1997. Individual studies reported a large variety of costs, calculated by varying means. Forty-four studies (56%) reported unadjusted costs[22 26 27 30 32-36 38-43 46 48-50 52-56 58 63-68 72 75 81-83 86-88 90 92-94 99], 21 (26%) adjusted costs[10 23-25 29 31 44 51 57 59-61 71 73 76-78 84 85 87 91], 11 a combination of adjusted and unadjusted[28 37 45 47 62 69 70 74 79 80 97], two unadjusted and predicted[95 96] and one predicted costs[98]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy and/or healthcare claims data (97%)[10 22-29 31-52 55 57 59-88 92-97]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data and disease state specific recommended guidelines. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 51 studies (63%) reporting nonadherence based on this measure[24 25 28 29 32-36 40-44 46 47 49-51 55 57 58 60-64 67-78 81 82 86-88 92-97]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (11%)[31 37 45 48 52 79 80 83-85], with all other studies utilizing an array of measures including self-report[98], urine testing[56], observational assessment[99], time to discontinuation[59], cumulative possession ratio[23], disease specific medication management guidelines[66 89], Morisky 4-Item scale[53], medication gaps[38],
prescription refill rates[22 27] and medication supplies[10]. The main characteristics of the included studies are summarized in eTable 2.

3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75 87 93], 59 of medium[10 22-26 28-32 34-36 38 39 41-48 53-56 58 59 61-64 66 67 69 70 72 73 76-82 84-86 88 89 91 94-99] and ten of low quality[27 49 60 65 68 74 83 90 92]. Scores ranged from 26.1% to 87.5% (mean 62.6%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [71]. The item ‘the choice of discount rate is stated and justified’ was applicable only to studies covering a time period of more than one year; all studies that cover more than one year failed to identify or explain why costs had not been discounted. Details of the analysis and interpretation of results were lacking in the majority of studies resulting in medium or low quality scores.

Through utilization of Drummond’s distinguishing characteristics of healthcare evaluations criteria[20] it is apparent that no full economic evaluation was conducted in any of the included studies. All studies performed partial economic evaluations of varying extents. The classification of economic evaluations resulted in 59 cost description studies (74% of those included), 15 cost outcome descriptions and five cost analysis studies (eTable 2).

3.4 Medication nonadherence and costs

The cost analysis of studies (figure 2 and figure 3) reported annual medication nonadherence costs incurred by the patient per year. The adjusted total cost of nonadherence across all disease groups ranged from $949 to $52,341, while the unadjusted total cost ranged from $669 to $162,699. Figure 2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by patients across disease groups where three or more studies were included for review. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Many different indicators were used to estimate medication nonadherence costs with no clear definition of what was incorporated in each cost component. The composition of included costs to estimate total cost or total healthcare cost varied significantly between studies thus indicators were grouped for analysis based on the original studies classification of the cost. The main ones were total
cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (46%), medical costs (29%), emergency department costs (27%), and hospitalization costs (18%) (eTable 2). Avoidable costs (e.g., unnecessary hospitalizations, physician office visits and healthcare resource utilization) were not well defined with majority of studies failing to quantify these costs.

Lower levels of adherence across all measures (e.g., MPR, PDC) were generally associated with higher total costs. From those that reported total or total healthcare costs, 39 studies (49%) reported nonadherence costs to be greater than adherence costs[24 25 29 31 32 34 37-39 42 43 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported nonadherence costs to be less than adherence costs[23 26 36 44 59 66 81 92 94 95]. Four reported fluctuating findings based on varying nonadherence cost subcategories[33 48 67 93] and two studies reported conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total nonadherence costs and lower disease group specific nonadherence costs were reported in four studies[41 68 85 91], whereas Hansen et al[47] reported all cause total nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

The association between nonadherence and cost was determined through use of a variety of scaling systems. The most utilized methods were MPR and PDC. These measures could then further be subcategorized based on the percentage of adherence/nonadherence. The 80-100% category was classified as the most adherent group across both scales, with the most common definition of nonadherence being <80% MPR or PDC.

### 3.5 Cost of medication nonadherence via disease group

Cancer exhibited more than double the cost variation of all other disease groups ($114,101). Osteoporosis ($43,240 vs. $42,734), diabetes mellitus ($7,077 vs. $6,808) and mental health ($16,110 vs. $23,408) cost variations were similar between adjusted and unadjusted costs while cardiovascular disease adjusted costs were more than double unadjusted costs ($16,124 vs. $6,943). Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy and parkinson’s disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal conditions. Direct costs had greater economic bearing than indirect costs across all disease groups. Cost comparisons across disease groups are summarized in eTable 3.
3.5.1 Cardiovascular Disease

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [10 24 31 61 62 65 67 76 81 93 95 96]. Six studies reported adjusted costs [10 24 31 61 62 76] with annual costs being extrapolated for two of these [31 61]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs [10 31 61 62 76], medical costs [10 24 31 61 76] and outpatient costs [31 62]. The annual economic cost of nonadherence ranged from $3,347 to $19,472. Sokol et al [10] evaluated the economic impact of medication nonadherence across three cardiovascular conditions; hypertension, hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined, pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups. Total costs and medical costs were lower for the adherent groups of hypertension and hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.

Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total costs of nonadherence ranging from $1,433 to $8,377 [65 67 81 93 95 96]. Rizzo et al [65] reported cost findings through subgroup analysis of five conditions. For all conditions the total healthcare costs were higher for nonadherent groups compared with adherent. While Zhao et al [81], categorized participants into adherence subgroups; finding that total healthcare costs were lower for the nonadherent population. The remaining studies used five key indicators to determine the economic impact: inpatient costs [67 93], outpatient costs [67 93], pharmacy costs [67 95 96], medical costs [95 96] and hospitalization costs [95 96].

3.5.2 Mental Health

The analyses used to report the economic impact of medication nonadherence in mental health varied widely. Eleven of 14 studies provided a total nonadherence cost estimate in mental health [23 25 27 52 59 66 73 82 91 98 99], with annual cost data being extrapolated for four of these [27 66 82 99]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from $3,252 to $19,363 [23 25 59 60 73 91]. Bagalman et al [25] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs while Robertson et al [82] highlighted the association between medication nonadherence and incarceration, with findings indicating incarceration and arrest costs are higher for worsening degrees of nonadherence. All other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication nonadherence were pharmacy
costs, inpatient costs, outpatient costs and hospitalization costs.

The total unadjusted cost for medication nonadherence ranged from $2,512 to $25,920 as reported in four studies. Becker et al. used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%, <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al. outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

### 3.5.3 Diabetes mellitus:

Eleven studies reported a cost measurement of the impact of medication nonadherence with reference to the health system and the individual. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819. One study reported total costs in relation to subgroup analysis based on MPR level, and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients. Curtis et al. utilized a diabetic population to report all cause costs, with nonadherence costs being higher than adherence costs across all outcome indicators bar pharmacy costs.

A further four studies reported unadjusted cost findings with an additional four studies reporting unadjusted costs in combination with adjusted values. Unadjusted total healthcare costs and/or total costs ranged from $1,142 to $7,951. Extrapolated annual costs were determined for two studies based on cost data presented.

The most prominent indicators used to determine costs were pharmacy costs, outpatient costs, inpatient costs and hospitalization costs. All studies assessed the direct costs associated with medication nonadherence. One study evaluated the relationship between nonadherence and short term disability costs in addition to assessing direct costs.
3.5.4 Osteoporosis:

The cost of medication nonadherence in relation to osteoporosis was predominately examined through analysis of the direct costs associated with nonadherence using total healthcare costs and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department costs. Two studies further assessed the economic impact of nonadherence through evaluation of fracture related costs [48 88]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [28 79 80 87]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[28] using MPR 20% interval increases and the two studies conducted by Zhao et al[79 80] using PDC, with ≥80% classified as high adherence, 50-79% medium adherence and <50% low adherence. In the studies conducted by Zhao et al[79 80], total healthcare costs were highest for the medium adherence group ($41,402 and $44,190) followed by the highest adherence group ($37,553 and $43,863), and lowest for the low adherence group ($34,019 and $43,771). These annual costs were extrapolated from study data. In contrast, Briesacher et al[28] modelled the subgroup analyses against the lowest adherence group (<20% MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from $669 to $43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In the three studies that reported the lowest level of nonadherence to be PDC <50%, the cost of this category ranged from $16,938 to $43,404 [48 79 80].

One study examined only the medical costs of nonadherence through MPR subgroup analysis in commercial and Medicare supplemental populations. The findings were that, for all levels of nonadherence, costs of nonadherence were higher for Medicare supplemental patients [46].

3.5.5 Respiratory Disease:

The majority of studies reported unadjusted cost of medication nonadherence, with significant variation in the method of adherence classification[36 38 53 64 89]. Two studies used MPR[36 64], one the Morisky 4-Item scale[53], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[89] and one a 37 day gap in claims data[38]. Joshi et al[53] reported on the indirect costs of medication nonadherence through consideration of losses in total productivity costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs. Delea et al[36] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[64] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the
lowest subgroup of adherence across all measures ranged from $804 to $36,259. Contrastingly Davis et al[85] utilized adjusted costs across four sub classifications of PDC adherence ranges to demonstrate that nonadherence costs were lower than adherence costs in all costing outcomes reported except hospitalization costs.

3.5.6 Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient utilizing the MPR method [44 57 71]. Of these, two reported the total cost ($12,085 and $37,151)[44 71] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalization costs to be $42,854 while Kane et al[54] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

3.5.7 Epilepsy:

Three studies reported the economic impact of medication nonadherence in epilepsy. All reported unadjusted costs using an MPR cut off of <80%[35 42 43]. The main economic indicators used to assess total costs were inpatient costs ($2,289 to $6,874), emergency department visit costs ($331 to $669) and pharmacy costs ($442 to $1,067). Davis et al[35] modelled the costs of the nonadherent group against the adherent group. The annual costs reported by Faught et al[43] were extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from $1,866 to $22,673.

3.5.8 HIV/AIDS:

The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all three studies was similar [26 32 63]. Two of the three studies examined the costs only for HIV[26 32], while Pruitt et al[63] assessed the cost in AIDS as well as HIV. The total unadjusted costs for nonadherent HIV patients ranged from $16,957 to $30,068 with one study further categorizing patients with HIV as having either a high viral load or low viral load[26]. The total cost of nonadherence in AIDS was $30,523[63]. All studies used comparable indicators (total cost, inpatient cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
3.5.9 Parkinson’s Disease:

The direct costs associated with Parkinson’s disease were assessed in all three studies. The unadjusted total cost ranged from $10,988 to $52,023 [34 37 72]. Wei et al[72] further sub-grouped patients into MPR adherence percentage categories, and found that costs increased in all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that $10,290 could be attributed to medication nonadherence annually[37].

3.5.10 Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence[50], one assessed only the medical costs[69] and one examined the direct costs in commercial and Medicare supplemental patient populations[78]. Zhao et al[78] reported the adjusted annual cost in the commercial population to be $22,609, and in the Medicare supplemental group, $28,126. Ivanova et al[50] reported only unadjusted costs and the annual total cost of $3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

3.5.11 Cancer:

Two studies evaluated the effects of medication nonadherence in cancer[33 75]. One study reported total annual costs of $119,416[75], while the other gave a subgroup analysis based on classified adherence levels[33]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs ($162,699 and $67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

3.5.12 Addiction:

The adjusted annual total healthcare cost of medication nonadherence was reported as $53,504[56] while the unadjusted cost ranged from $16,996 to $52,213 [56 70 86]. Leider et al[56] reported the main contributors to this cost to be outpatient costs ($10,829) and pharmacy costs ($8,855), whereas Tkacz et al[70] and Ruetsch et al[86] reported them to be inpatient costs ($28,407 and $5,808) and outpatient costs ($15,460 and $5,743).
3.5.13 Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of $138,525[55]. The economic indicators used to derive this cost were inpatient costs ($16,192), outpatient costs ($111,100), emergency department visit costs ($801) and pharmacy costs ($3,538).

3.5.14 Blood conditions:

Candrilli et al[29] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of $13,458 for nonadherence classified as MPR <80%.

3.5.15 All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[47 50 61 64 85 99]. Eleven studies reported on economic indicators without giving total cost or total healthcare cost[22 45 46 54 55 57 60 81 83 90 99], and one study reported on costs per episode of nonadherence[90].

The adjusted cost of medication nonadherence was reported in 14 studies with an estimated range of $5,271 to $52,341 [10 29 31 57 59-61 71 76 77 84 85 87 91]. Sokol et al[10] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[61] reported only using MPR level breakdown.

Fifteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of $1,037 to $53,793 [22 41 46 50 54 55 58 64-66 68 81 83 90 99]. A further four studies reported adjusted and unadjusted costs[37 45 47 97]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).

3.6 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of
required statistical parameters in particular standard deviation[100]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.
4 Discussion

This systemic review broadens the scope of knowledge associated with the economic impact of medication nonadherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication nonadherence. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesize costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication nonadherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to nonadherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to
medication nonadherence thus enabling greater planning in terms of health policy to help
counteract increasing avoidable costs.

The economic, clinical and humanistic consequences of medication nonadherence will continue to
grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to
adately address the determinants of adherence through utilization of effective health
interventions. Haynes et al [101] highlights that “increasing the effectiveness of adherence
interventions may have a far greater impact on the health of the population than any improvement
in specific medical treatments”. Improving medication adherence provides an opportunity for major
cost savings to healthcare systems. Predictions of population health outcomes through utilization of
treatment efficacy data need to be used in conjunction with adherence rates to inform planning and
project evaluation[4]. The correlation between increased nonadherence and higher disease
prevalence should be used to inform policy makers to help circumvent avoidable costs to the
healthcare system.

The metric of adherence estimation varied substantially within and across disease groups; likely
affecting the comparisons between studies. However, Hess et al [102], who compared six key
adherence measures on the same study participants, found that the measures produced similar
adherence values for all participants, although PDC and continuous measure of medication gaps
produced slightly lower values. While this highlights the comparability of the measures of
medication nonadherence, it further justifies the need to agree on consistent methods for
estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used
in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with
those found recently by Sattler et al [103]. Even though the measures of medication nonadherence
may be comparable, the definition of MPR and the cut-off points to define nonadherence differed
significantly. Dragomir et al[95] defined MPR as the total days’ supply of medication dispensed in the
period, divided by the follow up period, with the assumption of 100% adherence during
hospitalization; Wu et al[76] removed the number of hospitalized days from the calculation; and
Pittman et al[61] calculated the total number of days between the dates of the last filling of a
prescription in the first six months in a given year and the first filling of a prescription in the 365 days
before the last filling. Nonadherence could also be further classified into subcategories within MPR
and PDC based on percentages. Thirty studies defined nonadherence as MPR< 80%, and 12 studies
categorized nonadherence into varying percentage subgroups. While Karve et al[104] validated the
empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent
hospitalizations in patients across a broad array of chronic diseases, 76 of the 79 studies included in
this review examined more than just hospitalization costs as an indicator metric. Further research is
required to identify and standardize nonadherence thresholds using other outcomes such as
laboratory, productivity and pharmacy measures.

Within the 79 studies covered, 35 different indicators were used to measure the cost of
nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a
meta-analysis was impossible. It is imperative that a standardized approach be established to
measure and report the economic impact of medication nonadherence. The core outcome set must
take into consideration the perspective of the intended audience and the proportion of
nonadherence cost that is attributable to each outcome to determine an appropriate model[105].
The critical indicators based on the findings of this review include total costs, pharmacy costs,
inpatient costs, outpatient costs, emergency department visit costs, medical costs and
hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes
include short term disability costs, workers compensation costs, paid time off costs, absenteeism
costs and productivity costs. We suggest that further analysis of the contribution of each outcome to
the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future
research.

Many studies have examined the relationship between nonadherence and economic outcomes using
a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such
as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for
example, did greater adherence result in reduced costs and improved health outcomes, or was the
patient healthier initially and more capable of being adherent? A longitudinal design is needed to
overcome this limitation.

Economic evaluations inform decisions on how to best make use of scarce societal health resources
through offering an organized consideration of the range of possible alternative courses of action
and the evidence of the likely effects of each[20]. While none of the studies taken separately could
inform a choice between alternative courses of action, they did provide key evidence for decision
makers about costs associated with medication nonadherence. Pharmacy claims data were utilized
by the majority of studies to model cost estimates. Three-quarters of the studies were classified as
cost descriptions, providing a cost or outcome overview of the health consequences associated with
nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall
conclusions that are able to be drawn and emphasized the need for future study design to
incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106]
highlighted the need for more information on the consequences of nonadherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Of the seventy nine included studies, sixty six of the studies were conducted in the United States. Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and disease groups. Comparison of costs between healthcare systems is difficult as no two are the same and as healthcare is generally more expensive in the United States cost estimates may not reflect average values. Thus caution needs to be taken when interpreting results however findings help to represent the significance of the economic burden medication nonadherence plays. Analysis of studies not conducted in the United States support the finding that generally medication nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication nonadherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the inclusion criteria[22 23 65 73 74 98]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between nonadherence and increasing healthcare costs.
5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilization of existing data could help to better define costs and provide valuable input into the development of an economic framework to standardize the economic impact of medication nonadherence.
6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data extraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

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Competing interests: None declared

Data sharing statement: All data from systematic review available in paper and supplementary material.

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73. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003;11(12):817-22 doi: 10.2165/00115677-200311120-00006[published Online First: Epub Date].
92. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;49:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]].


Figure Legends

Figure 1: PRISMA Flow Diagram
The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2768 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication nonadherence using original cost data. Intervention studies were required to report baseline data. Seventy nine original studies met the inclusion criteria.

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
Encompass the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 1: Annual Unadjusted Medication Nonadherence Costs per patient per year
Encompass the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy and addiction only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.
Figure 1: Flow diagram of references identified, retrieved and included in the systematic review
Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year

*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.

** All cause costs: mixed disease state studies

209x297mm (300 x 300 DPI)
Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year

*Disease groups with three or more studies were included. Epilepsy and Addiction only included three studies limiting the range of costs.

** All cause costs: mixed disease state studies

209x297mm (300 x 300 DPI)
### eTable 1 Search Strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Strategy</th>
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<tbody>
<tr>
<td>Scopus</td>
<td>( TITLE-ABS-KEY ( medication AND compliance OR patient AND compliance ) ) AND ( TITLE-ABS-KEY ( statistical AND model ) ) AND ( TITLE-ABS-KEY ( health AND care AND cost ) )</td>
</tr>
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</table>
Table 2: Studies identified with costs reported by adherence level and disease group

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Objective</th>
<th>Study Characteristics</th>
<th>Adherence (as reported in paper)</th>
<th>Outcomes/Indicators</th>
<th>Results (USD, 2015)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
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<td><strong>Cardiovascular Disease</strong></td>
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</tbody>
</table>
To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalization costs.

**Design:** Retrospective cohort study
**Follow Up:** 3 years
**Sample Size:** 56896 (A:38217, NA:18679)

**Measure:** MPR
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent
**Method of Assessment:** pharmacy claims data

**Total Healthcare Costs**
- **Pharmacy Costs**
- **Medical Costs**
- **Hospitalization Costs**

**Type of Costs:** unadjusted and predicted
disease state specific and hospitalized patients

**Cost of Nonadherence:**
- **Unadjusted Disease state specific:**
  - THC: $7165 ($6900.87), PC: $1800 ($1733.64), MC: $1370 ($1319.50), HC: $3995 ($3847.73)
  - *Total*: $12,733.39
- **Unadjusted Hospitalized patients:**
  - THC: $17397 ($16755.67), PC: $2685 ($2586.02), MC: $2608 ($2511.86), HC: $12104 ($11657.79)
  - *Total*: $48,422.38
- **Predicted disease state specific:**
  - THC: $3877 ($3734.08)
- **Predicted Hospitalized patient:**
  - THC: $11715 ($11283.13)

**Currency Year:** CAD, 2006

**Quality:** medium

---

Dragomir et al [4]
2010
Canada

To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.

**Design:** Retrospective cohort study
**Follow Up:** 3 years
**Sample Size:** 55134 (A:28549, NA:26585)

**Measure:** MPR
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent
**Method of Assessment:** pharmacy claims data

**Total Healthcare Costs**
- **Pharmacy Costs**
- **Medical Costs**
- **Hospitalization Costs**

**Type of Costs:** unadjusted and predicted
disease state specific and hospitalized patients

**Cost of Nonadherence:**
- **Unadjusted Disease state specific:**
  - THC: $6243 ($6175.76), PC: $2506 ($2479.01), MC: $1241 ($1227.63), HC: $2496 ($2469.12)
  - *Total*: $12,445.59
- **Unadjusted Hospitalized patients:**
  - THC: $14566.40, PC: $3374 ($3337.66), MC: $2475 ($2448.34), HC: $8876 ($8780.40)
  - *Total*: $34,159.71
- **Predicted disease state specific:**
  - THC: $3877

**Currency Year:** CAD, 2005

**Quality:** medium
Pittman et al[6]
2011
US
To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.

<table>
<thead>
<tr>
<th>Design: Retrospective cohort study</th>
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<tbody>
<tr>
<td>Follow Up: 18 months</td>
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<tr>
<td>Sample Size: 381422</td>
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<th>Measure: MPR</th>
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<td>Classification:</td>
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<tr>
<th>Total Healthcare Costs</th>
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<tr>
<td>Pharmacyst</td>
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<td>Medical Costs</td>
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Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2009
Cost of Nonadherence: all cause:
THC(>80):$6798.67 ($7505.66),
THC(60-79):$7072.67 ($7808.16),
THC(<59):$401.33 ($8170.99),
PC(>80):$1767.33 ($1951.11),
PC(60-79):$1789.33 ($1975.40),
PC(<59):$1937.33 ($2138.79),
MC(>80):$4472.67 ($4937.78),
MC(60-79):$4840.67 ($5344.05,
MC(<59):$5138.67 ($5673.04)
Disease state specific:
PC(>80):$558.67 ($616.77),
PC(60-79):$442.67 ($488.70),
PC(<59):$185.33 ($359.16),
MC(>80):$1596.67 ($1762.71),
MC(60-79):$1722 ($1901.07),
MC(<59):$1792.67 ($1979.09)

Quality: medium
Classification: cost description

Pittman et al[7]
2010
US
To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and

<table>
<thead>
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<td>Follow Up: 2 years</td>
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<table>
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<tr>
<th>Measure: MPR</th>
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<tr>
<td>Classification:</td>
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<td>MPR ≥ 80 = adherent, MPR &gt;60&lt;79% = moderate adherence, MPR &lt;59 = low adherence</td>
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<tr>
<th>Total Healthcare Costs</th>
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<tr>
<td>Outpatient Costs</td>
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<td>ED Costs</td>
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<tr>
<td>Pharmacy Costs</td>
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<tr>
<td>Hospitalization Costs</td>
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</tbody>
</table>

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence: Adjusted:
THC(>80):$761 ($8077.79),
THC(60-79):$7530 ($8377.05),
THC(<59):$2930 ($8199.05),
OC(>80):$3890 ($3771.34),
OC(60-79):$3705 ($4121.77),

Quality: medium
Classification: cost description
<table>
<thead>
<tr>
<th>Costs</th>
<th>Method of Assessment</th>
<th>Pharmacy claims data</th>
</tr>
</thead>
</table>

**Rizzo et al[8]**

1997  
US  

To investigate variations in compliance with four classes of antihypertensive agents- diuretics, ACEIs, CCBs and β-

**Design:** Retrospective cohort study  
**Follow Up:** 12 months  
**Sample Size:** 7211(P:2668, NC:3101, NP:649, T:793)  

**Measure:** ordinary least square regression analysis  
**Classification:** >80% = persistent, ≥30<80% = non-compliance, <30%  

**Total Healthcare Costs**  

**Type of Costs:** unadjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 1994  
**Cost of Nonadherence:** All cause: THC(>80): $841 ($509.66), THC(30-80): $944 ($1037.26),
blockers and the healthcare costs associated with various degrees of compliance.

Method of Assessment: pharmacy claims data

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<td>Renal:</td>
<td>THC(&gt;80): $2135 ($3190.98),</td>
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<tr>
<td></td>
<td>THC(30-80): $2488 ($3718.58),</td>
</tr>
<tr>
<td></td>
<td>THC(&lt;30): $2529 ($3799.86),</td>
</tr>
<tr>
<td>Acute MI:</td>
<td>THC(&gt;80): $358 ($2029.67),</td>
</tr>
<tr>
<td></td>
<td>THC(30-80): $1711 ($2557.27),</td>
</tr>
<tr>
<td></td>
<td>THC(&lt;30): $1752 ($2618.55),</td>
</tr>
<tr>
<td>Diabetes:</td>
<td>THC(&gt;80): $770 ($1150.85),</td>
</tr>
<tr>
<td></td>
<td>THC(30-80): $1123 ($1678.44),</td>
</tr>
<tr>
<td></td>
<td>THC(&lt;30): $1164 ($1739.72),</td>
</tr>
<tr>
<td>CHF:</td>
<td>THC(&gt;80): $698 ($1043.23),</td>
</tr>
<tr>
<td></td>
<td>THC(30-80): $1051 ($1570.83),</td>
</tr>
<tr>
<td></td>
<td>THC(&lt;30): $1092 ($1632.11),</td>
</tr>
<tr>
<td>Angina:</td>
<td>THC(&gt;80): $702 ($1049.21),</td>
</tr>
<tr>
<td></td>
<td>THC(30-80): $1055 ($1576.81),</td>
</tr>
<tr>
<td></td>
<td>THC(&lt;30): $1096 ($1638.09),</td>
</tr>
</tbody>
</table>


To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study

Follow Up: 12 months

Sample Size: 137277

Diabetes:
- TH(80-100): $950 ($1413.23)
- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
- TH(<19): $674 ($1067.23)

Hypertension:
- TH(80-100): $950 ($1413.23)
- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
- TH(<19): $674 ($1067.23)

Diabetes:
- TH(80-100): $950 ($1413.23)
- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
- TH(<19): $674 ($1067.23)

Hypertension:
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- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
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- TH(80-100): $950 ($1413.23)
- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
- TH(<19): $674 ($1067.23)

CHF:
- TH(80-100): $950 ($1413.23)
- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
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Angina:
- TH(80-100): $950 ($1413.23)
- TH(60-79): $798 ($1230.83)
- TH(40-59): $757 ($1187.23)
- TH(20-39): $716 ($1134.23)
- TH(<19): $674 ($1067.23)

Quality: medium

Classification: cost description
Hypercholesterolemia:
(≥80: 1754, 60-79: 520,
40-59: 324, 20-39: 216,
<19: 167)
CHF: (≥80: 518, 60-79:
107, 40-59: 82, 20-39:
70, <19: 86)

PC(20-39): $1877 ($2624.89),
PC(40-59): $1970 ($2754.94),
PC(60-79): $2121 ($2966.11),
PC(80-100): $2510 ($3510.10),
MC(1-19): $15186 ($21236.82),
MC(20-39): $11200 ($15662.61),
MC(40-59): $11008 ($15394.10),
MC(60-79): $9363 ($13093.66),
MC(80-100): $6377 ($8917.90),

Hypertension:
TC(1-19): $9747 ($13630.66),
TC(20-39): $11238 ($15715.75),
TC(40-59): $9491 ($13272.66),
TC(60-79): $8929 ($12486.73),
TC(80-100): $8386 ($11272.38),
PC(1-19): $916 ($1280.98),
PC(20-39): $952 ($1331.32),
PC(40-59): $1123 ($1570.46),
PC(60-79): $1271 ($1777.43),
PC(80-100): $1817 ($2540.98),
MC(1-19): $8831 ($12349.69),
MC(20-39): $10286 ($14384.43),
MC(40-59): $8368 ($11702.20),
MC(60-79): $7658 ($10709.31),
MC(80-100): $6570 ($9187.80),

Hypercholesterolemia:
TC(1-19): $20916 ($31265.45),
TC(20-39): $27982 ($31162.40),
TC(40-59): $26756 ($39447.91),
TC(60-79): $8412 ($11763.74),
TC(80-100): $86752 ($9442.31),
PC(1-19): $2067 ($1492.14),
PC(20-39): $1152 ($1611.01),
<table>
<thead>
<tr>
<th>Age Group</th>
<th>PC Cost ($USD)</th>
<th>MC Cost ($USD)</th>
<th>CHF Cost ($USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC(1-19)</td>
<td>$1247 (1743.86)</td>
<td>$9849 ($13773.30)</td>
<td>$23964 ($33512.38)</td>
</tr>
<tr>
<td>PC(20-39)</td>
<td>$1736 ($2427.70)</td>
<td>$6830 ($9551.39)</td>
<td>$19188 ($26833.40)</td>
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<tr>
<td>PC(40-59)</td>
<td>$1972 ($2757.74)</td>
<td>$5509 ($7704.04)</td>
<td>$26311 ($36794.54)</td>
</tr>
<tr>
<td>PC(60-79)</td>
<td>$1736 ($2427.70)</td>
<td>$6676 ($9336.03)</td>
<td>$29785 ($41652.74)</td>
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<tr>
<td>PC(80-100)</td>
<td>$1972 ($2757.74)</td>
<td>$3412 ($4771.50)</td>
<td>$22164 ($30995.18)</td>
</tr>
<tr>
<td>MC(1-19)</td>
<td>$55 ($76.91)</td>
<td>$22003 ($30770.03)</td>
<td>$22003 ($30770.03)</td>
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<tr>
<td>MC(20-39)</td>
<td>$165 ($230.74)</td>
<td>$17133 ($23959.59)</td>
<td>$26373 ($36881.24)</td>
</tr>
<tr>
<td>MC(40-59)</td>
<td>$285 ($398.56)</td>
<td>$24103 ($33706.77)</td>
<td>$26373 ($36881.24)</td>
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<tr>
<td>MC(60-79)</td>
<td>$3412 ($4771.50)</td>
<td>$26373 ($36881.24)</td>
<td>$26373 ($36881.24)</td>
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<tr>
<td>MC(80-100)</td>
<td>$3412 ($4771.50)</td>
<td>$19056 ($26648.81)</td>
<td>$19056 ($26648.81)</td>
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</tbody>
</table>

Disease state specific: Diabetes:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>PC Cost ($USD)</th>
<th>MC Cost ($USD)</th>
<th>CHF Cost ($USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC(1-19)</td>
<td>$8867 ($12400.03)</td>
<td>$6637 ($9120.67)</td>
<td>$26373 ($36881.24)</td>
</tr>
<tr>
<td>TC(20-39)</td>
<td>$8712 ($12916.90)</td>
<td>$6522 ($9120.67)</td>
<td>$26373 ($36881.24)</td>
</tr>
<tr>
<td>TC(40-59)</td>
<td>$3291 ($4797.63)</td>
<td>$6291 ($9120.67)</td>
<td>$26373 ($36881.24)</td>
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<tr>
<td>TC(60-79)</td>
<td>$4570 ($6390.90)</td>
<td>$2165 ($320.74)</td>
<td>$4570 ($6390.90)</td>
</tr>
<tr>
<td>Condition</td>
<td>TC (Age Group)</td>
<td>Amount ($)</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>TC (1-19)</td>
<td>$6878 ($6821.62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TC (20-39)</td>
<td>$5062 ($8477.39)</td>
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</tr>
<tr>
<td></td>
<td>TC (40-59)</td>
<td>$5297 ($7407.57)</td>
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</tr>
<tr>
<td></td>
<td>TC (60-79)</td>
<td>$5262 ($7358.63)</td>
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</tr>
<tr>
<td></td>
<td>TC (80-100)</td>
<td>$4871 ($6811.84)</td>
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</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>TC (1-19)</td>
<td>$6888 ($6932.50)</td>
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<tr>
<td></td>
<td>TC (20-39)</td>
<td>$6999 ($6990.84)</td>
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</tr>
<tr>
<td></td>
<td>TC (40-59)</td>
<td>$5385 ($5349.06)</td>
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<tr>
<td></td>
<td>TC (60-79)</td>
<td>$5541 ($7748.79)</td>
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<tr>
<td></td>
<td>TC (80-100)</td>
<td>$53924 ($5487.51)</td>
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</table>

PC (Age Group) Amount ($)  

<table>
<thead>
<tr>
<th>PC (Age Group)</th>
<th>Amount ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC (1-19)</td>
<td>$78 ($109.08)</td>
</tr>
<tr>
<td>PC (20-39)</td>
<td>$213 ($297.87)</td>
</tr>
<tr>
<td>PC (40-59)</td>
<td>$373 ($521.62)</td>
</tr>
<tr>
<td>PC (60-79)</td>
<td>$603 ($843.26)</td>
</tr>
</tbody>
</table>

MC (Age Group) Amount ($)  

<table>
<thead>
<tr>
<th>MC (Age Group)</th>
<th>Amount ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC (1-19)</td>
<td>$4847 ($6778.27)</td>
</tr>
<tr>
<td>MC (20-39)</td>
<td>$5973 ($8375.32)</td>
</tr>
<tr>
<td>MC (40-59)</td>
<td>$5113 ($7150.26)</td>
</tr>
<tr>
<td>MC (60-79)</td>
<td>$4977 ($6960.07)</td>
</tr>
<tr>
<td>MC (80-100)</td>
<td>$5438 ($6129.39)</td>
</tr>
</tbody>
</table>
To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patient with complicated and uncomplicated hypertension and to

| Design | Retrospective cohort study |
| Sample Size | 15206 (not specified) |
| Follow Up | 3.3 years |

**Measure:** MPR

- **Classification:**
  - MPR < 80 = undersupply
  - MPR > 120 = oversupply

**Method of Assessment:** pharmacy claims data

**Total Healthcare Costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Disease State Specific</th>
<th>Cost of Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Costs</td>
<td>THC: $6032.50 ($7830.11)</td>
<td>IC: $2067 ($2682.94)</td>
</tr>
<tr>
<td>Outpatient Costs</td>
<td>OC: $3965 ($5146.52)</td>
<td>PC: $130 ($168.74)</td>
</tr>
<tr>
<td>Pharmacy Costs</td>
<td><strong>$6032.50 ($7830.11)</strong></td>
<td><strong>$2067 ($2682.94)</strong></td>
</tr>
</tbody>
</table>

**Quality:** medium
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Classification</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Costs</td>
<td>adjusted</td>
<td>medium</td>
</tr>
<tr>
<td>Short term disability cost</td>
<td>disease state specific</td>
<td></td>
</tr>
<tr>
<td>Workers compensation cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid time off cost</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mental Health**

*Bagalman et al [13]*

2010

US

To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.

**Design:** Retrospective cohort study

**Follow Up:** 1 year

**Sample Size:** 1258 (A:444, NA:814)

**Measure:** MPR

**Classification:**

- MPR≥80 = adherent
- MPR <80 = nonadherent

**Method of Assessment:** pharmacy claims data

**Total Costs**:

- **TC:** $6894 ($8273.53)
- **STDC:** $2134 ($2561.03)
- **WCC:** $762 ($914.48)
- **PTOC:** $3998 ($4798.03)

**Type of Costs:** adjusted

**Classification:** disease state specific

**Currency Year:** USD, 2005

**Cost of Nonadherence:** TC:$6894 ($8273.53), STDC:$2134 ($2561.03), WCC:$762 ($914.48), PTOC:$3998 ($4798.03)

**Quality:** medium

---

*Becker et al [14]*

Examine treatment

**Design:** Retrospective

**Measure:** Total Costs

**Type of Costs:** unadjusted

**Quality:** low

---

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
2007 US outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries. cohort study Follow Up: 2 years Sample Size: 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505) prescription refill rate Classification: 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence Method of Assessment: pharmacy claims data Classification: disease state specific Currency Year: USD, 2006 Cost of Nonadherence:
TC(75-100):$13564 ($15792.91), TC(50-74):$13772 ($16035.09), TC(25-49):$15792 ($18387.03), TC(<25):$16156 ($18810.84)

Eaddy et al[15]
2005 US To evaluate the effect of partial compliance of patients with prescribed oral atypical and conventional antipsychotic agents and the corresponding impact on resource utilisation. Design: Retrospective database analysis Follow Up: 1 year Sample Size: 7864 (<80%:2655, 80-125%:2655, >125%:144) continuous multiple interval medications available Classification: <80% = partially compliant, 80-125% = compliant, >125% = overly compliant Method of Assessment: pharmacy claims data Measure: Inpatient costs Total costs Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence:
IC:$3780 ($4906.39), OC:$504 ($654.19), PC:$1872 ($2429.83), MC:$6228 ($8083.86), POC:$1944 ($2523.29) OtC:$12 ($15.58)

Gilmer et al[16]
2004 US To evaluate the relationship between adherence to Design: Retrospective database analysis Follow Up: 1 year Measure: Total costs Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 1999
treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.

**Sample Size:** 1619
- <49%: 388
- 50-79%: 259
- 80-100%: 664
- >110%: 308

**Classification:**
- <49% = nonadherent
- 50-79% = partially adherent
- 80-100% = adherent
- >110% = excess medication fillers

**Method of Assessment:** pharmacy claims data

**Pharmacy costs**
- TC: $8168, (61261.74),
- OC: $3464, (4776.04),
- PC: $1542, (2126.05),
- HC: $3413, (4705.72),

**Cost of Nonadherence:**
- TC: £55.43 ($94.87)
- Disease state specific:
  - TC: £5846.29 ($9964.10)
  - IC: £2740.57 ($4670.88)
  - OC: £1082.86 ($1845.57)
  - PC: £1630.29 ($2778.58)
  - HC: £337.14 ($574.60)

**Method of Assessment:** observational assessment

**Type of Costs:** unadjusted

**Quality:** medium

**Classification:** cost description

---

**Hong et al** [17]
2011
UK

To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.

**Design:** Prospective observational study
**Follow Up:** 21 months
**Sample Size:** 1341 (A: 1024, NA: 317)

**Measure:** assessed by treating psychiatrist

**Classification:** adherent vs. nonadherent

**Method of Assessment:** observational assessment

**Total costs**
- Inpatient costs
- Outpatient costs
- Pharmacy costs
- Hospitalization costs

**Type of Costs:** unadjusted

**Classification:** all cause and disease state specific

**Currency Year:** GBP, 2008

**Quality:** medium

**Classification:** cost description

---

**Jiang et al** [18]
2015
US

To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalization by controlling potential sources of endogeneity.

**Design:** Retrospective cohort study
**Follow Up:** 2 years
**Sample Size:** 32374 (A: 11642, NA: 20732)

**Measure:** PDC

**Classification:** (PDC≥80% = adherent, PDC<80% = nonadherent)

**Method of Assessment:** medical and

**Total costs**
- Pharmacy costs
- Medical services costs

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2011

**Quality:** low

**Classification:** cost description

---

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Joe et al[19]
2016
South Korea

To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 7848

Pharmacy claims data

Measure: Total costs
Percentage of days of psychiatric prescription (PDP)
Classification: Total costs
PDP≥80% = adherent,
PDP<80% = nonadherent;
persistent = continued medication without interruption ≥ 56 day, non-persistent = at least one medication interruption > 56 days

Method of Assessment: Total costs
Health insurance data

Quality: medium
Classification: all cause and disease state specific
Currency Year: USD, 2011
Cost of Nonadherence: all cause:
TC:$4961 ($5271.40)
Disease state specific:
TC:$3061 ($3252.50)

Knapp et al[20]
2004
UK

To assess the relative impact of non-adherence and other factors associated with resource use and costs incurred by people with schizophrenia.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 658
(A:549, NA:109)

Pharmacy claims data

Measure: Total costs
Self-report
Classification: Total costs
adherent vs. nonadherent

Method of Assessment: Total costs
Health insurance data

Quality: medium
Classification: all cause and disease state specific
Currency Year: GBP, 2001
Cost of Nonadherence: all cause:
TC:£57580 ($116434.12)
IC:£6714 ($13576.57),
ESC:£1603 ($3241.47)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offord et al[21]</td>
<td>2013</td>
<td>US</td>
<td>To quantify early nonadherence to antipsychotic medications in patients</td>
<td>Retrospective</td>
<td>1 year</td>
<td>1462 (A:589, NA:873)</td>
<td>time to discontinuation</td>
<td>adherent vs. nonadherent</td>
<td>adjusted</td>
<td>TC:$15400 ($17132.34), OC:$5773 ($6422.40), PC:$3777 ($4201.87), HC:$5850 ($6508.06)</td>
<td>medium</td>
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<tr>
<td></td>
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<td>with schizophrenia and its impact on short-term antipsychotic adherence,</td>
<td>cohort study</td>
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<tr>
<td></td>
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<td>healthcare utilisation and costs.</td>
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<tr>
<td>Offord et al[22]</td>
<td>2013</td>
<td>US</td>
<td>To examine the impact of medication adherence on healthcare utilisation</td>
<td>Retrospective</td>
<td>1 year</td>
<td>354 (A:126, NA:228)</td>
<td>MPR ≥ 70 = high adherence, MPR &lt; 70 = low adherence</td>
<td>Pharmacy costs</td>
<td>adjusted</td>
<td>IC:$9053 ($10071.37), PC:$4267 ($4746.99), Disease state specific: IC:$2468 ($2745.62), PC:$1085 ($1207.05)</td>
<td>low</td>
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<tr>
<td></td>
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<td>among Medicare insured schizophrenia patients.</td>
<td>cohort study</td>
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<tr>
<td>Robertson et al[23]</td>
<td>2014</td>
<td>US</td>
<td>To examine the impact of the combination of treatment utilization and</td>
<td>Retrospective</td>
<td>90 days</td>
<td>1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)</td>
<td>Total costs</td>
<td>Pharmacy costs</td>
<td>TC(90/90):$28068 ($33495.65), TC(60/90):$21720 ($25920.11), TC(30/90):$21084 ($25161.12), TC(0/90):$2156 ($14936.28)</td>
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<td>medication possession on arrest and incarceration outcomes and on costs.</td>
<td>cohort study</td>
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<tr>
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<td>IC(30/90)</td>
<td>IC(0/90)</td>
<td>OC(90/90)</td>
<td>OC(60/90)</td>
<td>OC(30/90)</td>
<td>OC(0/90)</td>
<td>EDC(90/90)</td>
<td>EDC(60/90)</td>
<td>EDC(30/90)</td>
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<td>costs</td>
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<td>$592</td>
<td>$6468</td>
<td>$4152</td>
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<td>$1136</td>
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<td>IC(90/90)</td>
<td>$14520.99</td>
<td>$12014.90</td>
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<td>$7718.75</td>
<td>$4954.89</td>
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<td>$12014.90</td>
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<td>$4152</td>
<td>$2916</td>
<td>$1136</td>
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<td>$2549.05</td>
<td>$114.56</td>
<td>$128.88</td>
<td>$171.85</td>
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<td>Arrest costs</td>
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<td>$1404</td>
<td>$1596</td>
<td>$516</td>
<td>$2100</td>
<td>$1404</td>
<td>$1596</td>
<td>$516</td>
<td>$2100</td>
<td>$1404</td>
<td>$1596</td>
<td>$516</td>
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<tr>
<td>Incarceration costs</td>
<td>$5592</td>
<td>$3468</td>
<td>$2232</td>
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<td>$96</td>
<td>$6673.35</td>
<td>$4138.63</td>
<td>$2663.61</td>
<td>$1174.28</td>
<td>$2506.09</td>
<td>$1675.50</td>
<td>$1904.63</td>
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</table>

Robinson et al[24] To determine if the design was effective, the researchers used a retrospective design. The measure used was total costs, and the type of costs was unadjusted. The quality of the study was medium.
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Study Title</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>US</td>
<td>To examine the relationship of medication non-adherence to hospital use and costs among newly diagnosed patients.</td>
<td>Retrospective database analysis</td>
<td>6 months</td>
<td>60386 (A:11526, NA:8860)</td>
<td>Pharmacy claims, Medicaid data, observational assessment</td>
<td>one or more quarters without a claim = nonadherent</td>
<td>all cause and disease state specific</td>
<td>unadjusted</td>
<td>USD, 2004</td>
</tr>
<tr>
<td>2001</td>
<td>US</td>
<td>To examine the relationship of medication non-adherence to hospital use and costs among severely mentally ill clients.</td>
<td>Retrospective database analysis</td>
<td>1 year</td>
<td>619 (A:413, NA:206)</td>
<td>Pharmacy claims, previous study data</td>
<td>one or more quarters without a claim = nonadherent</td>
<td>all cause and disease state specific</td>
<td>unadjusted</td>
<td>USD, 1990</td>
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<tr>
<td>2003</td>
<td>US</td>
<td>To evaluate the economic impact of antidepressant</td>
<td>Retrospective database analysis</td>
<td>6 months</td>
<td></td>
<td>MPR</td>
<td>MPR≥70% =</td>
<td>Disease state specific</td>
<td>adjusted</td>
<td>USD, 1999</td>
</tr>
</tbody>
</table>
Diabetes
An et al.[27] 2014 Korea
This study evaluated the association between medication adherence and clinical/economic outcomes in patients with type II diabetes mellitus in the republic of Korea over a 3 year period.

Design: Prospective cohort study
Follow Up: 3 years
Sample Size: 608 (A:472, NA:136)

Measure: MPR
Classification: MPR≥90% = adherent, MPR<90% = nonadherent
Method of Assessment: pharmacy claims data

Medical costs
Cost of Nonadherence:
TC: $11815 ($16290.09)
PC: $1123 ($1548.35)
MC: $10692 ($14741.74)

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2007

Quality: medium
Classification: cost description

Buysman et al.[28] 2017 US
To examine the impact of real world adherence on glycaemic control in type 2 diabetes patients treated with canagliflozin.

Design: Retrospective database analysis
Follow Up: 12 months
Sample Size: 2261 (A:1215, NA:1046)

Measure: PDC
Classification: PDC≥80% = highly adherent, PDC<80% = less than highly adherent
Method of Assessment: healthcare claims data

Pharmacy costs
Cost of Nonadherence:
TC: $1657.11 ($1884.14)
OC: $1413.99 ($1608.20)
HC: $243.11 ($276.12)

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2014

Quality: low
Classification: cost description

Curtis et al.[29] 2017 US
Examine the association between adherence to glucose lowering agents and...

Design: Retrospective analysis
Follow Up: 3 years
Sample Size: 228074

Measure: PDC
Classification: PDC≥80% = adherent
Method of Assessment: healthcare claims data

Total costs
Cost of Nonadherence:
TC: $7225 ($7297.39)
PC: $4660 ($4706.69)

Type of Costs: adjusted
Classification: all cause
Currency Year: USD, 2014

Quality: medium
Classification: cost description
Egede et al. [30] 2012 US
To examine the longitudinal effects of medication nonadherence on key costs and estimate potential savings from increased adherence using novel methodology that accounts for shared correlation among cost categories.

**Method of Assessment:** healthcare claims data

**Measure:** MPR

**Classification:**

<table>
<thead>
<tr>
<th>PDC&lt;80% = nonadherent</th>
<th>costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute care costs</td>
<td>TC:$38633 ($39020.09)</td>
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<tr>
<td>OC: $16964 ($17134),</td>
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</tr>
<tr>
<td>PC: $9390 ($9484.08),</td>
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<tr>
<td>ACC:$12153 ($12274.77)</td>
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</tr>
</tbody>
</table>

Gentil et al. [31] 2015 Canada
To examine healthcare costs associated with adherence to oral antihyperglycemic agents and the effects of depression and anxiety disorders on these in older adults with type 2 diabetes.

**Method of Assessment:** pharmacy claims data

**Measure:** MPR

**Classification:**

<table>
<thead>
<tr>
<th>Type of Costs: unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs</td>
</tr>
<tr>
<td>Inpatient costs</td>
</tr>
<tr>
<td>Outpatient costs</td>
</tr>
<tr>
<td>Pharmacy costs</td>
</tr>
</tbody>
</table>

**Type of Costs:**
- all cause and disease state specific

**Currency Year:** USD, 2006

**Cost of Nonadherence:**
- IC:$14515.24 ($17886.40)
- OC: $3599.27 ($4434.16)
- PC: $1073.12 ($1322.42)

**Quality:** high

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For peer review only - [http://bmjopen.bmj.com/site/about/guidelines.xhtml](http://bmjopen.bmj.com/site/about/guidelines.xhtml)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagen et al[32]</td>
<td>2014</td>
<td>US</td>
<td>To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/ short term disability costs</td>
<td>Retrospective, observational cohort analysis</td>
<td>PDC</td>
<td>PDC≥80% = compliant, PDC&lt;80% = noncompliant</td>
<td>Healthcare costs</td>
<td>Adjusted all cause: PC: $14979 ($13221.30), POC: $568 ($517.24)</td>
<td>Medium</td>
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<td>Classification: cost description</td>
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<td></td>
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<td></td>
<td>Healthcare costs</td>
</tr>
<tr>
<td>Hansen et al[33]</td>
<td>2010</td>
<td></td>
<td>To compare all cause total health care costs</td>
<td>Retrospective, cohort study</td>
<td>MPR</td>
<td></td>
<td>Type of Costs: adjusted and unadjusted</td>
<td>Adjusted all cause: PC: $1668 ($2065.99), Adjusted disease state specific: HC: $7642 ($9465.39), PC: $512 ($760.50), MC: $5974 ($7399.40), STDC: $1840 ($2279.03)</td>
<td>Medium</td>
</tr>
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<td></td>
<td>Unadjusted all cause: PC: $1727 ($2139.06), Unadjusted disease state specific: HC: $6919 ($8569.88), PC: $785 ($972.30), MC: $5192 ($6430.82), STDC: $1717 ($2126.68)</td>
</tr>
</tbody>
</table>
and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.

**Follow Up:** 2 years  
**Sample Size:** 108592 (A:63830, NA:44762)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  
**Type of Costs:** inpatient costs  
**Cost of Nonadherence**: adjusted all cause: THC:$13228 ($15911.01), adjusted disease state specific: THC:$2284 ($2741.04)  
**Currency Year:** USD, 2005

**Hong et al[34]**  
2011  
South Korea  
To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.  
**Design:** Retrospective, cohort study  
**Follow Up:** 3 years  
**Sample Size:** 40082 (A:11800, NA:28282)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  
**Total costs:** hospitalization costs  
**Type of Costs:** unadjusted  
**Cost of Nonadherence**  
**Currency Year:** KRW, 2007  
**Classification:** disease state specific  
**Quality:** medium

**Jha et al[35]**  
2012  
US  
How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or decreased health care costs?  
**Design:** Retrospective, observational claims analysis  
**Follow Up:** unclear  
**Sample Size:** 135639 (A:99976, NA:35663)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  
**Total costs:** hospitalization costs  
**Type of Costs:** adjusted  
**Cost of Nonadherence**  
**Currency Year:** USD, 2011  
**Classification:** disease state specific  
**Quality:** high
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

White *et al*[36] 2004 US

To assess the relationship between diabetic medication adherence, total healthcare costs and utilisation with patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease.

| Design: Retrospective, database analysis | Measure: MPR Classification:  |
|Follow Up: 1 year | MPR≥95%, MPR>75%<95%, MPR<75% |
|Sample Size: 67029 (>95:20170, 75-95: 14074, <75:16713) | Method of Assessment: pharmacy claims data |

| Total costs Pharmacy costs Non-pharmacy costs |
|---|---|---|
| **Type of Costs:** adjusted and unadjusted Classification: disease state specific |
| **Currency Year:** USD, 2000 |
| **Cost of Nonadherence:** adjusted: |
| TC(≥95): $4835 ($6518.17), |
| TC(75-95): $5314 ($7163.92), |
| TC(<75): $5706 ($7692.38), |
| PC(≥95): $1429 ($1926.47), |
| PC(75-95): $1157 ($1559.78), |
| PC(<75): $762 ($1027.27), |
| NPC(≥95): $3406 ($4591.70), |
| NPC(75-95): $4157 ($5604.14), |
| NPC(<75): $4944 ($6665.11) |
| **Unadjusted:** |
| TC(≥95): $4809 ($6483.12), |
| TC(75-95): $5333 ($7189.53), |
| TC(<75): $5605 ($7556.22) |

| Quality: low Classification: cost analysis |

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

**Design:** Retrospective, cohort study  
**Follow Up:** 1 year  
**Sample Size:** 2354 (A:830, NA:1524)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total healthcare costs</th>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
<th>Pharmacy costs</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>MPR ≥80% = high compliance</td>
<td>$1402 ($1890.07), PC(≥95)</td>
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<tr>
<td>MPR &lt;80% = low compliance</td>
<td>$1153 ($1554.38), PC(75-95)</td>
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<td>Subgroup Analysis:</td>
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<td>commercial and Medicare supplemental</td>
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<td>pharmacy claims data</td>
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<td>Cost of Nonadherence:</td>
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<td>IC(com): $2851 ($14692.74),</td>
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<td>IC(med): $754 ($7863.85),</td>
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<td>OC(com): $11888 ($13841.50),</td>
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<td>OC(med): $10598 ($12339.52),</td>
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<td>PC(com): $2667 ($8926.88),</td>
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<td>PC(med): $270 ($8464.65),</td>
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<td>Adjusted disease state specific:</td>
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<td>IC(com): $232 ($2598.77),</td>
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<td>IC(med): $2006 ($3034.23),</td>
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<td>OC(com): $1389 ($2315.84),</td>
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<td>OC(med): $231 ($1433.28),</td>
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<td>PC(com): $3451 ($1689.44),</td>
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<tr>
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<td>DPNP:</td>
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<td>THC(com): $3565 ($4150.82),</td>
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<td>THC(med): $2384 ($2775.75),</td>
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</tbody>
</table>
Osteoporosis

Briesacher et al[38]

2007

US

To assess rates of osteoporotic fractures and health care utilization as a function of bisphosphonate compliance in usual clinical practice.

**Design:** Retrospective, cohort study

**Follow Up:** 3 years

**Sample Size:** 17988 (not specified)

**Measure:** MPR

**Classification:** 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent

**Method of Assessment:** pharmacy claims data

**Total costs**

**Inpatient costs**

**Outpatient costs**

**Pharmacy costs**

**Type of costs:** adjusted and unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2004

**Cost of Nonadherence**

Adjusted:

TC(80-100): $859 ($1063.96),
TC(60-79): $474 ($587.10),
TC(40-59): $151 ($187.03),
IC(80-100): $3233 ($4004.40),
IC(60-79): $856 ($1060.24),
IC(40-59): $6221 ($7705.34),
IC(20-39): $585 ($724.58),
OC(80-100): $445 ($551.18),
OC(60-79): $538 ($666.37),
OC(40-59): $236 ($292.31),
OC(20-39): $60 ($74.32),
PC(80-100): $997 ($1234.89),
PC(60-79): $5973 ($709.72),
PC(40-59): $402 ($497.92),
PC(20-39): $160 ($198.18)

Unadjusted:

TC(80-100): $1273 ($1576.74),
TC(60-79): $294 ($364.15),
TC(40-59): $573 ($709.72),
TC(20-39): $101 ($125.10),
IC(80-100): $883 ($1093.68),
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>MPR Classification</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Eisenberg et al[39]</td>
<td>2015</td>
<td>US</td>
<td>Retrospective claims study</td>
<td>2 years</td>
<td>27905</td>
<td>MPR</td>
<td>(≥70% = compliant, &lt;70% = noncompliant)</td>
<td>Inpatient costs</td>
<td>unadjusted</td>
<td>medium</td>
</tr>
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<td>(A:11368, NA:16537)</td>
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<td></td>
<td>Outpatient costs</td>
<td>all cause and disease state specific</td>
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<td>ED costs</td>
<td>USD, 2012</td>
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<td>Pharmacy costs</td>
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<td>Physician office visit costs</td>
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<td>Total costs</td>
<td>Cost of Nonadherence: all cause:</td>
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<td>TC: $7237 ($7550.72),</td>
<td>commercial:</td>
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<td>IC: $1986 ($2072.09),</td>
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<td>OC: $2057 ($2146.17),</td>
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<td>EDC: $258 ($269.18),</td>
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<td>PC: $2197 ($2292.24),</td>
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<td>POC: $738 ($769.99)</td>
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<td>Disease state specific:</td>
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<td>TC: $674 ($703.22),</td>
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<td>IC: $334 ($348.48),</td>
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<td>OC: $77 ($80.34),</td>
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<td>EDC: $5 ($5.22),</td>
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<td>PC: $213 ($222.23),</td>
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<td>POC: $44 ($45.91)</td>
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<tr>
<td>Halpern et al[40]</td>
<td>2011</td>
<td>US</td>
<td>Retrospective analysis</td>
<td>540 days</td>
<td>21655</td>
<td>MPR</td>
<td>(≥80% = high adherence,)</td>
<td>Medical costs</td>
<td>unadjusted</td>
<td>medium</td>
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<td>Type of Costs:</td>
<td>Classification: all cause</td>
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<td>Commercial:</td>
<td>cost outcome description</td>
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<td></td>
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<td>Currency Year: USD, 2006</td>
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<td>Cost of Nonadherence:</td>
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<td>USD, 2006</td>
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</tr>
</tbody>
</table>
with occurrence of closed fracture, all cause medical costs and all cause hospitalizations.

Hazel-Fernandez et al[41] 2013 US

To evaluate the healthcare utilisation patterns of medicare part D beneficiaries newly initiating teriparatide and to assess the association of medication adherence and persistence with bone fracture.

Design: Retrospective cohort study
Follow Up: 12 months
Sample Size: 761
(≥80%:163, ≥50<80%:57, <50%:541)

Method of Assessment:
pharmacy claims data

Measure: PDC
Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence)

Total healthcare costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs

Type of Costs: unadjusted
disease state specific and fracture related

Classification: cost outcome description

Currency Year: USD, 2010

Cost of Nonadherence:
Disease state specific:
THC(≥80): $21033 ($22942.39),
THC(50-80): $25574 ($27895.62),
THC(<50): $15528 ($16937.64),
IC(≥80): $2198 ($2397.54),
IC(50-80): $8448 ($9214.91),
IC(<50): $4897 ($5341.55),
OC(≥80): $5151 ($5618.61),
OC(50-80): $6439 ($7023.54),
OC(<50): $5806 ($6333.07),
EDC(≥80): $211 ($230.15),
EDC(50-80): $330 ($359.96),
EDC(<50): $465 ($507.21),
PC(≥80): $13472 ($14695),
PC(50-80): $10358 ($11298.31),
PC(<50): $4361 ($4756.89)

Fracture related:
THC(≥80): $12670 ($13820.19),
THC(50-80): $9292 ($10135.53),
THC(<50): $4419 ($4820.16),
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Total Costs</th>
<th>Type of Costs</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huybrechts et al[42]</td>
<td>2006</td>
<td>US</td>
<td>To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.</td>
<td>Retrospective cohort study</td>
<td>5 years</td>
<td>38120 (A:9530, NA:28590)</td>
<td>MPR</td>
<td>(≥80% = compliant, &lt;50% = noncompliant)</td>
<td>TC: $7200 ($9706.44), MC: $1476 ($1989.84), InstC: $5736 ($7732.80)</td>
<td>Unadjusted</td>
<td>Low</td>
</tr>
<tr>
<td>Kjellberg et al[43]</td>
<td>2016</td>
<td>Denmark</td>
<td>To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of noncompliance with health care resource use and cost.</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>38234 (A:26806, NA:11428)</td>
<td>MPR</td>
<td>(≥70% = compliant, &lt;70% = noncompliant)</td>
<td>TC: €4933 ($6209.58), MC: €3471 ($4369.20), InstC: €754 ($949.12)</td>
<td>Adjusted (all cause and disease state specific)</td>
<td>High</td>
</tr>
<tr>
<td>Modi et al[44]</td>
<td>2015</td>
<td>Denmark</td>
<td>To evaluate compliance with osteoporosis medications</td>
<td>Retrospective cohort study</td>
<td></td>
<td></td>
<td>MPR</td>
<td></td>
<td>TC: $10810 ($11791.34), MC: $7420 ($8093.59), PC: $2068 ($2255.73)</td>
<td>Unadjusted</td>
<td>Medium</td>
</tr>
</tbody>
</table>
US osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance

Follow Up: 1 year
Sample Size: 27913 (A:23430, NA:34483)

(≥80% = compliant, <80% = noncompliant)

Method of Assessment: healthcare claims data

Outpatient costs
ED costs
Pharmacy costs
Medical costs
Other costs

state specific
Currency Year: USD, 2011
Cost of Nonadherence: all cause:
TC:$11749 ($12484.12),
IC:$8768 ($9316.60),
OC:$3945 ($4191.83),
EDC:$104 ($110.51),
PC:$2981 ($3167.52),
MC:$8768 ($9316.60),
OtC:$997 ($1059.38)

Disease state specific:
TC:$630 ($669.42),
IC:$443 ($470.72),
OC:$158 ($167.89),
EDC:$3 ($3.19),
PC:$325 ($345.33),
OtC:$26 ($27.63)

Outcome description

Olsen et al[45] 2013 Denmark To assess the association between refill compliance and all cause health care costs.

Design: Retrospective observational study
Follow Up: 2 years
Sample Size: 47176 (not specified)

Measure: MPR
Classification:
(≥80% = optimal compliance,
>50<80% = suboptimal compliance, <50% = low compliance)

Method of Assessment: pharmacy claims data

Fracture costs

Type of Costs: unadjusted
Classification: fracture site specific
Currency Year: DKK, 2010
Cost of Nonadherence:
Hip fracture:
FC(50-80): kr817575.50 ($74531.41),
FC(<50): kr54954 ($549987.04)
Spine fracture:
FC(50-80): kr174700 ($21568.12),
FC(<50): kr26472 ($27959.14)
Humerus fracture:
FC(50-80): kr117776.50 ($14540.12),
FC(<50): kr95217.50 ($98173.70)
Forearm fracture:
FC(50-80): kr463024 ($57162.70),
FC(<50): kr5072.50 ($665.81)

Quality: medium
Classification: cost analysis
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Design</th>
<th>Measure</th>
<th>Type of Costs</th>
<th>Sample Size</th>
<th>Total Healthcare Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Sunyecz et al</td>
<td>Retrospective observational study</td>
<td>MPR</td>
<td>unadjusted</td>
<td>32944</td>
<td>FC(50-80): kr19261.50 (-$2377.93), FC(&lt;50): kr684067.50 ($84451.66)</td>
<td>THC: kr23660 ($28394.52), IC: kr18839 ($22608.81), OC: kr10063 ($12074.27), EDC: kr832 ($988.49), PC: kr6941 ($8329.94), RC: kr1079 ($1294.91)</td>
<td>Low</td>
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<tr>
<td>2014</td>
<td>Zhao et al</td>
<td>Retrospective cohort study</td>
<td>PDC</td>
<td>adjusted and unadjusted</td>
<td>824</td>
<td>THC(≥80): kr34428 ($37553.4), THC(50-80): kr37956 ($41401.68), THC(&lt;50): kr1188 ($34019.28), IC(≥80): kr7848 ($8233.20), IC(50-80): kr11520 ($1256.80), IC(&lt;50): kr12556 ($12605.04)</td>
<td>Adjusted: kr44428 ($50125.4), IC: kr4542.45, PC: kr918 ($1101.70), RC: kr184 ($220.82)</td>
<td>Medium</td>
</tr>
</tbody>
</table>
To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients. Design: Retrospective observational cohort study Follow Up: 36 months Sample Size: 1568 (≥80: 783, 50-80%: 382, <50%: 403) Measure: PDC Classification: (≥80% = high, 50-80% = medium, <50% = low) Method of Assessment: pharmacy claims data Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence:

Adjusted:

THC(≥80): $40212 ($43862.52), THC(50-80): $40512 ($44189.76), THC(<50): $40128 ($43770.84), IC(≥80): $8136 ($8874.60), IC(50-80): $12060 ($13154.76), IC(<50): $15444 ($43404.36), OC(≥80): $12924 ($14097.24), OC(50-80): $14928 ($16283.16), OC(<50): $17568 ($19162.80), PC(≥80): $7844 ($8754.76), PC(50-80): $11352 ($12382.56), PC(<50): $16192 ($17688.80), Unadjusted:

THC(≥80): $37464 ($40865.04), THC(50-80): $35076 ($38260.20), THC(<50): $29484 ($32160.60), IC(≥80): $7092 ($7735.80), IC(50-80): $11100 ($12107.64), IC(<50): $10632 ($11597.16), OC(≥80): $9900 ($10798.68), OC(50-80): $11352 ($12382.56), OC(<50): $11988 ($13076.28), PC(≥80): $20484 ($22343.52), PC(50-80): $12624 ($13770), PC(<50): $6864 ($7487.16)
To assess the association between adherence levels to different inhaled corticosteroid/long acting β₂-adrenergic agonist and COPD exacerbation rates and costs in commercially insured population

**Design:** Observational cohort study  
**Follow Up:** 12 months  
**Sample Size:** 13657  
(≥80%: 1898, ≥50<80%: 1971, ≥30 <50%: 2443, <30% :7345)

**Measure:** PDC  
**Classification:** (≥80 = adherent,  
≥50<80% = mildly nonadherent, ≥30 <50% = moderately nonadherent, <30% highly nonadherent)

**Method of Assessment:** commercially insured healthcare claims data  

**Total costs**  
**Outpatient costs**  
**Pharmacy costs**  
**Hospitalization costs**

**Type of Costs:** adjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 2014  
**Cost of Nonadherence:**

- **All cause:**
  - TC(≥80): $22546 ($22772.24),  
  - TC(50-80): $22545 ($25800.95),  
  - TC(30-50): $24303 ($24546.51),  
  - TC(<30): $25148 ($25399.98),  
  - OC(≥80): $7816 ($7894.31),  
  - OC(50-80): $8225 ($8307.41),  
  - OC(30-50): $8365 ($8448.81),  
  - OC(<30): $8857 ($8945.74),  
  - PC(≥80): $7954 ($8033.70),  
  - PC(50-80): $7900 ($8033.70),  
  - PC(<50): $7900 ($8033.70)

**Unadjusted:**

- **THC(≥80):** $42768 ($46650.48),  
  - THC(50-80): $36780 ($40118.88),  
  - THC(<50): $39792 ($43404.36),  
  - IC(≥80): $7620 ($8311.80),  
  - IC(50-80): $12228 ($13338.12),  
  - IC(<50): $15768 ($17199.48),  
  - OC(≥80): $14580 ($15903.60),  
  - OC(50-80): $12108 ($13207.20),  
  - OC(<50): $15324 ($16715.16),  
  - PC(≥80): $20568 ($22435.20),  
  - PC(50-80): $12444 ($13573.68),  
  - PC(<50): $8700 ($9489.84)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Delea et al[50]

2008
US

To assess the association between adherence with fluticasone propionate/salmeterol combination product in a single inhaler and asthma care utilisation and costs in asthma

**Design:** Retrospective longitudinal cohort study

**Follow Up:** 24 months

**Sample Size:** 12907

(≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)

**Measure:** MPR

**Classification:** (≥75, 50-75%, 25-50%, <25%)

**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2003

**Cost of Nonadherence:**

- **Total costs**
  - Outpatient costs
    - PC(≥80): $6862 ($6930.76),
    - PC(30-50): $5485 ($5539.96),
    - PC(<30): $4935 ($4439.04),
    - HC(≥80): $6106 ($6167.51),
    - HC(50-80): $9391 ($9485.09),
    - HC(30-50): $9171 ($9262.89),
    - HC(<30): $10849 ($10957.70)

  - ED costs
    - PC(≥80): $7953 ($8123.67),
    - PC(50-80): $9171 ($9262.89),
    - PC(30-50): $6623 ($6689.36),
    - PC(<30): $4395 ($4439.04),
    - HC(≥80): $6106 ($6167.51),
    - HC(50-80): $9391 ($9485.09),
    - HC(30-50): $9171 ($9262.89),
    - HC(<30): $10849 ($10957.70)

  - Other costs
    - PC(≥80): $1947 ($1966.51),
    - PC(50-80): $1997 ($2017.01),
    - PC(30-50): $1947 ($1966.51),
    - PC(<30): $1569 ($1584.72),
    - HC(≥80): $1947 ($1966.51),
    - HC(50-80): $1997 ($2017.01),
    - HC(30-50): $1947 ($1966.51),
    - HC(<30): $1569 ($1584.72)

**Quality:** medium

**Classification:** cost description
To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and received palivizumab in accordance with the dosing schedule recommended by the American Academy of Paediatrics in 2006 versus those who did not.

**Diehl et al [51]**

**Design:** Retrospective claims analysis

**Follow Up:** 7 months

**Sample Size:** 245 (A:73, NA:172)

**Measure:** 37 day gap in claims

**Classification:** (>37 day gap in claims = noncompliant)

**Method of Assessment:** pharmacy claims data

**Total costs**

**Pharmacy costs**

**Services costs**

**TC:** $19093.46 ($21656.12),

**PC:** $7647.40 ($8673.81),

**SC:** $11604.03 ($13161.45)

**Quality:** medium

**Classification:** cost description

---

Examine the association of medication adherence with workplace productivity and health related quality of life in asthma patients.

**Joshi et al [52]**

**Design:** quantitative analysis

**Follow Up:**

**Sample Size:** 385 (high:150, medium:73, low: 162)

**Measure:** Morisky scale

**Classification:** 0 = high adherence, 1-2 = medium adherence, >2 = low adherence

**Method of Assessment:**

**Total productivity cost**

**Absenteeism costs**

**Presenteeism costs**

**Type of costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2002

**Cost of Nonadherence**

**TPC(0):** $1260.90 ($1571.73),

**TPC(1-2):** $428.50 ($1854.17),

**TPC(>2):** $873.10 ($1392.87),

**AbC(0):** $638.70 ($822.53),

**AbC(1-2):** $608.90 ($790.34),

**Quality:** medium

**Classification:** cost outcome description
Miravitlles et al[53] 2013 Spain

To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).

**Design:** multicentre, retrospective, observational study

**Follow Up:** 18 months

**Sample Size:** 1365 (A:246, NA:1119)

**Measure:** GOLD 2007 Guidelines

**Classification:** (adherent, nonadherent)

**Method of Assessment:** GOLD guidelines

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** EUR, 2009

**Cost of Nonadherence:**

- **ED costs:** €40.83 ($57.91),
- **Pharmacy costs:** €771.50 ($1094.27),
- **Physician office visit costs:** €106.29 ($150.76),
- **Hospitalization costs:** €101.61 ($144.12),
- **Primary care costs:** €123.84 ($175.65),
- **Interdisciplinary visit costs:** €321.44 ($455.92),
- **Medical test costs:** €36.66 ($51.99),
- **Radiology costs:** €24.24 ($34.38),
- **Laboratory costs:** €17.35 ($24.61)

**Quality:** medium

Quittner et al[54] 2014 US

To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.

**Design:** retrospective, cohort study

**Follow Up:** 2 years

**Sample Size:** 3287

**Measure:** MPR

**Classification:** (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence)

**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2011

**Cost of Nonadherence:**

- **All cause:**
  - THC(≥80%): $55749.50 ($38244.05),
  - THC(50-80%): $45031.50 ($48173.73),
  - THC(<50%): $20284.50 ($53793.28)
- **Disease state specific:**
  - THC(≥80%): $23764 ($25422.22),
  - THC(50-80%): $16380.50 ($19965.49),
  - THC(<50%): $10937.50 ($14233.13)

**Quality:** medium
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Hospitalization Costs</th>
<th>Type of Costs</th>
<th>Classification</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter et al [55]</td>
<td>2011</td>
<td>US</td>
<td>To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.</td>
<td>Retrospective, observational cohort claims analysis</td>
<td>12 months</td>
<td>638 (A:466, NA:172)</td>
<td>Number of infusions in 12 month period</td>
<td>Adherent: ≥7 infusions</td>
<td>Unadjusted</td>
<td>Disease state specific</td>
<td>USD, 2007</td>
<td>THC(50-80): $33132.50 ($35444.44), THC(&lt;50): $33894 ($36259.07)</td>
</tr>
<tr>
<td>Gosselin et al [56]</td>
<td>2009</td>
<td>US</td>
<td>To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.</td>
<td>Retrospective cohort study</td>
<td>12 months</td>
<td>41837 (A:28321, NA:13516)</td>
<td>MPR (≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Total costs</td>
<td>Adjusted</td>
<td>Disease state specific</td>
<td>USD, 2003</td>
<td>TC: $9497 ($12085.43), IC: $2116 ($2692.72), OC: $5458 ($6945.59), PC: $1922 ($2445.85), MC: $7575 ($9639.58)</td>
</tr>
<tr>
<td>Kane et al [57]</td>
<td>2009</td>
<td>US</td>
<td>To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by patients.</td>
<td>Retrospective cohort analysis</td>
<td>12 months</td>
<td>571 (A:375, NA:196)</td>
<td>Number of infusions in 12 month period</td>
<td>Adherent: ≥8 infusions</td>
<td>Unadjusted</td>
<td>All cause and disease state specific</td>
<td>USD, 2004</td>
<td>Outpatient: $6679 ($8272.62), ED: $314 ($388.92), Medical: $16128 ($19977.40), Hospitalization: $16128 ($19977.40)</td>
</tr>
</tbody>
</table>
Mitra et al[58] 2012 US
To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.

Design: retrospective, observational cohort study
Follow Up: 12 months
Sample Size: 1693 (A:476, NA:1216)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Method of Assessment: pharmacy claims data

Assessment: health claims data

Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Ancillary costs
Non-pharmacy costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2010

Cost of Nonadherence:
All cause:
PC:$1541.60 ($1681.55)

Disease state specific:
IC:$28726.65 ($31334.47),
OC:$1145.67 ($1249.67),
EDC:$635.95 ($693.68),
AC:$4923.29 ($5370.23),
NPC:$14226.32 ($15517.79)

Quality: high
Classification: cost description

Wan et al[59] 2014 US
To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.

Design: retrospective cohort analysis
Follow Up: 360 days
Sample Size: 1646 (A:674, NA:972)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Method of Assessment: pharmacy claims data

Total costs
Total healthcare costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs

Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2009

Cost of Nonadherence:
All cause: $47411 ($52341.27),
TC:$47411 ($52341.27),
THC:$32524 ($35903.47),
IC:$17634 ($19467.76),
OC:$10909 ($12043.43),
EDC:$458 ($505.63),
PC:$18410 ($20324.46)

Disease state specific:

Quality: high
Classification: cost description
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
<th>Cost Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al[60]</td>
<td>2008</td>
<td>US</td>
<td>To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.</td>
<td>Retrospective claims analysis</td>
<td>12 months</td>
<td>10,892 (A:6,644, NA:4,248)</td>
<td>MPR</td>
<td>(≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Pharmacy claims data</td>
<td>Total costs</td>
<td>Inpatient costs</td>
<td>ED costs</td>
<td>Pharmacy costs</td>
<td>Other</td>
<td>Other pharmacy costs</td>
</tr>
<tr>
<td>Ettinger et al[61]</td>
<td>2009</td>
<td>US</td>
<td>To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.</td>
<td>Retrospective claims analysis</td>
<td>12 months</td>
<td>1,278 (A:758, NA:520)</td>
<td>MPR</td>
<td>(≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Pharmacy claims data</td>
<td>Total costs</td>
<td>Inpatient costs</td>
<td>ED costs</td>
<td>Pharmacy costs</td>
<td>Physician</td>
<td>Office visit costs</td>
</tr>
<tr>
<td>Faught et al[62]</td>
<td>2009</td>
<td>US</td>
<td>To study the impact of non-adherence to antiepileptic drugs</td>
<td>Retrospective observational open cohort design</td>
<td></td>
<td></td>
<td>MPR</td>
<td>(≥80% = adherent)</td>
<td>Pharmacy claims data</td>
<td>Total costs</td>
<td>Inpatient costs</td>
<td>Other</td>
<td>Pharmacy costs</td>
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<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Objective</td>
<td>Methodology</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
<td>Classification</td>
<td>Method of Assessment</td>
<td>Type of Costs</td>
<td>Currency Year</td>
<td>Cost of Nonadherence*</td>
<td>Quality</td>
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<td>(AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.</td>
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<tr>
<td>Barnett et al [63]</td>
<td>2011</td>
<td>US</td>
<td>To characterise the cost of HIV care including combination antiretroviral treatment.</td>
<td>Descriptive retrospective observational cohort study</td>
<td>4.65 years</td>
<td>33658 (A:24907, NA:8751)</td>
<td>&lt;80% = nonadherent</td>
<td></td>
<td>Pharmacy claims data</td>
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<tr>
<td>Cooke et al [64]</td>
<td>2014</td>
<td>US</td>
<td>To measure adherence to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors associated with ≥90% adherence.</td>
<td>Descriptive retrospective claims analysis</td>
<td>1 year</td>
<td>1896 (not specified)</td>
<td>≥90% = adherent, &lt;90% = nonadherent</td>
<td>Pharmacy claims data</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Objective</td>
<td>Study Design</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
<td>Classification</td>
<td>Cost of Nonadherence</td>
<td>Type of Costs</td>
<td>Quality</td>
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<tr>
<td>Pruitt et al[65]</td>
<td>2015</td>
<td>US</td>
<td>To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.</td>
<td>Retrospective cohort study</td>
<td>2 years</td>
<td>502 (A:56, NA:176)</td>
<td>MPR</td>
<td>≥90% = adherent, &lt;90% = nonadherent</td>
<td>Pharmacy costs</td>
<td>Unadjusted</td>
<td>Medium</td>
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<td>Disease state specific</td>
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<tr>
<td>Parkinson's Disease</td>
<td>2010</td>
<td>US</td>
<td>To assess the extent to which patients diagnosed with Parkinson's disease are non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.</td>
<td>Retrospective administrative claims study</td>
<td>12 months</td>
<td>3119 (A:1211, NA:1908)</td>
<td>MPR</td>
<td>≥80% = adherent, &lt;80% = nonadherent</td>
<td>Pharmacy costs</td>
<td>Unadjusted</td>
<td>Medium</td>
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<td>Disease state specific</td>
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<tr>
<td>Delea et al[67]</td>
<td>2011</td>
<td>US</td>
<td>To assess the associations between adherence to</td>
<td>Retrospective historical cohort study</td>
<td>12 months</td>
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<td>PDC</td>
<td>≥80% = adherent</td>
<td>Pharmacy costs</td>
<td>Adjusted and unadjusted</td>
<td>High</td>
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<td>All cause and disease state specific</td>
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</tbody>
</table>
levodopa/carbidopa/entacapone therapy and healthcare utilisation and costs.

Sample Size: 1215 (A:617, NA:598) satisfactory, <80% = unsatisfactory)

Method of Assessment: pharmacy claims data

Currency Year: USD, 2005

Cost of Nonadherence:
Adjusted all cause:
TC:$19686 ($23625.30),
IC:$5954 ($7145.43),
PC:$6391 ($7669.88),
OtC:$8795 ($10554.94)
Adjusted disease state specific:
TC:$8574 ($10289.71),
IC:$3705 ($4446.39),
PC:$3850 ($4620.41),
OtC:$1884 ($2261)
Unadjusted all cause:
TC:$19362 ($23236.46),
IC:$5463 ($6556.18),
PC:$6158 ($7390.26),
OtC:$7740 ($9288.82)
Unadjusted disease state specific:
TC:$9156 ($10988.18),
IC:$3238 ($3885.94),
PC:$3789 ($4547.20),
OtC:$2129 ($2555.03)

Measures: MPR
Classification: (>90<100% = high, 80-89% = moderate, ≤79% = low)

Method of Assessment: pharmacy claims data

Design: retrospective cross-sectional study
Follow Up: 19 months
Sample Size: 7583 (90-100%:3948, 80-89%:1456, ≤79%:2179)

Type of Costs: unadjusted
Classification: disease state specific

Costs:

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Total costs</th>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
<th>Pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC(90-100)</td>
<td>$36407</td>
<td>$36407</td>
<td>$36407</td>
<td>$36407</td>
</tr>
<tr>
<td>TC(80-89)</td>
<td>$43417</td>
<td>$43417</td>
<td>$43417</td>
<td>$43417</td>
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<tr>
<td>TC(≤79)</td>
<td>$45867</td>
<td>$45867</td>
<td>$45867</td>
<td>$45867</td>
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<tr>
<td>IC(90-100)</td>
<td>$15294</td>
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<tr>
<td>IC(80-89)</td>
<td>$21603</td>
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<tr>
<td>IC(≤79)</td>
<td>$24727</td>
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<td>OC(90-100)</td>
<td>$10155</td>
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<tr>
<td>OC(80-89)</td>
<td>$1884</td>
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<tr>
<td>OC(≤79)</td>
<td>$2129</td>
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</tr>
</tbody>
</table>

Quality: medium
Classification: cost description
Ivanova et al [69]

Musculoskeletal
2012
US

To compare the rates of severe relapse and total direct and indirect costs over a 2 year period between US based employees with MS who were adherent and non-adherent to disease modifying drugs.

Design: retrospective cohort study
Follow Up: 2 years
Sample Size: 648 (A:448, NA:200)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Method of Assessment: pharmacy claims data

Total costs
Total healthcare costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Medical costs
Short term disability costs
Absenteeism cost

OC(80-89): $11838 ($13426.86),
OC(≤79): $12889 ($14618.92),
PC(90-100): $10957 ($12427.61),
PC(80-89): $9976 ($11314.95),
PC(≤79): $8251 ($9358.42)

Quality: high
Classification: cost description

Tan et al [70]

2011
US

To assess the impact of treatment adherence on MS related hospitalizations

Design: retrospective cohort study
Follow Up: 12 months
Sample Size: 2446

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2007

Cost of Nonadherence:

All cause:
TC: $8079 ($9276.76),
THC: $6022 ($6830.25),
IC: $1030.50 ($1168.81),
OC: $3231 ($3664.65),
EDC: $143.50 ($162.76),
PC: $1617 ($1834.03),
MC: $4405.50 ($4996.79)

Disease state specific:
TC: $3005 ($3408.32),
IC: $505 ($572.78),
OC: $1710 ($1939.51),
EDC: $37 ($41.97),
PC: $753 ($854.07),
MC: $2252 ($2554.26)

Indirect:
STDC: $1234 ($1396.22),
AbC: $826 ($936.86)

Quality: medium
Classification: cost description
Zhao et al[71]  
2011  
US  
To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.  
**Design:** retrospective cohort analysis  
**Follow Up:** 12 months  
**Sample Size:** 5435  
(A:1744, NA:3691)  
**Measure:** MPR  
**Classification:**  
(≥80% = adherent, <80% = nonadherent)  
**Method of Assessment:** pharmacy claims data  

**Total costs**  
**Inpatient costs**  
**Outpatient costs**  
**Pharmacy costs**  

**Type of Costs:** adjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2008  
**Cost of Nonadherence:**  
Commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40)  
Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)  

**Quality:** medium  
**Classification:** cost analysis

Cancer  
Darkow et al[72]  
2007  
US  
Estimate the association between treatment interruptions and non-adherence with imatinib and healthcare costs for US managed care patients.  
**Design:** retrospective observational cohort analysis  
**Follow Up:** 12 months  
**Sample Size:** 267  
(≥95%:120, 90-95%:25, 50-90%:69, <50%:53)  
**Measure:** MPR  
**Classification:**  
(≥95% = very high, >90-95% = high, >50-90% = intermediate, <50% = low)  
**Method of Assessment:** pharmacy claims data  

**Total healthcare costs**  
**Inpatient costs**  
**Outpatient costs**  
**Pharmacy costs**  
**Medical costs**  
**Other pharmacy costs**  
**Other costs**  

**Type of Costs:** unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2004  
**Cost of Nonadherence:**  
Commercial: THC(≥95):$32250 ($52330.90), THC(90-95):$39236 ($48597.76), THC(50-90):$47770 ($67838.19), THC(<50):$71357 ($162698.93), IC(≥95):$1456 ($1431.82), IC(90-95):$362 ($1686.97), IC(50-90):$7096 ($23652.33), IC(<50):$8972 ($101035.18), OC(≥95):$9299 ($11517.75), OC(90-95):$11148 ($13807.93), OC(50-90):$7096 ($23652.33), OC(<50):$8972 ($101035.18)  

**Quality:** high  
**Classification:** cost description

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
To examine the association between adherence with imatinib and direct healthcare costs and resource utilisation

Design: retrospective observational cohort analysis
Follow Up: 12 months
Sample Size: 592 (A:350, NA:242)

Measure: MPR
Classification: (≥85% = high adherence, <85% = low adherence)

Method of Assessment: pharmacy claims data

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
TC:$107341 ($119415.73),
IC:$44498 ($49503.55),
OC:$34097 ($37932.55),
EDC:$248 ($275.90),
PC:$22846 ($25415.93),
OtPC:$5652 ($6287.79)

Quality: medium
Classification: cost description
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leider et al[74] 2011 US</td>
<td>To assess the economic burden of chronic opioid users and to determine whether opioid regimen nonadherence contributes to increased healthcare costs.</td>
<td>Design: retrospective claims based analysis</td>
<td>Follow Up: 12 months</td>
<td>Sample Size: 2100 (A:442, NA:1658)</td>
<td>Measure: urine testing</td>
<td>Classification: (positive test = nonadherent, negative test = adherent)</td>
<td>Method of Assessment: health claims data</td>
<td>Total healthcare costs</td>
<td>Inpatient costs</td>
<td>Outpatient costs</td>
<td>ED costs</td>
</tr>
<tr>
<td>Ruetsch et al[75] 2017 US</td>
<td>To examine patient characteristics and outcomes associated with nonadherence to buprenorphine and to identify specific patterns of nonadherent behaviour.</td>
<td>Design: cross sectional, retrospective analysis health claims data</td>
<td>Follow Up: 12 months</td>
<td>Sample Size: 477 (A:172, NA:305)</td>
<td>Measure: MPR</td>
<td>Classification: (≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Method of Assessment: health claims data</td>
<td>Total healthcare costs</td>
<td>Inpatient costs</td>
<td>Outpatient costs</td>
<td>ED costs</td>
</tr>
<tr>
<td>Tkacz et al[76] 2014 US</td>
<td>To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent</td>
<td>Design: retrospective cohort analysis</td>
<td>Follow Up: 12 months</td>
<td>Sample Size: 455 (A:146, NA:309)</td>
<td>Measure: MPR</td>
<td>Classification: (≥80% = adherent, &lt;80% = nonadherent)</td>
<td>Method of Assessment: pharmacy claims data</td>
<td>Total healthcare costs</td>
<td>Inpatient costs</td>
<td>Outpatient costs</td>
<td>ED costs</td>
</tr>
</tbody>
</table>
Metabolic conditions other than diabetes mellitus

Lee et al[77]: To assess the relationship between medication adherence and healthcare costs among US patients on dialysis given cinacalcet to manage secondary hypoparathyroidism.

- **Design:** Retrospective cohort study
- **Follow Up:** 12 months
- **Sample Size:** 4923 (A:1372, NA:1304)
- **Measure:** MPR
- **Classification:** (≥80% = high adherent, <80% = low adherent)
- **Method of Assessment:** Pharmacy claims data
- **Type of Costs:** Unadjusted
- **Classification:** All cause and disease state specific
- **Currency Year:** USD, 2010
- **Cost of Nonadherence:**
  - **All cause:**
    - PC: $3581 ($3906.09)
    - THC: $47868 ($52213.49)
    - IC: $26043 ($28407.20)
    - OC: $14173 ($15459.63)
    - EDC: $4058 ($4426.39)
    - PC: $3557 ($3879.91)
  - **Disease state specific:**
    - TC: $41058 ($44465.78)
    - IC: $26043 ($28407.20)
    - OC: $14173 ($15459.63)
    - EDC: $4058 ($4426.39)
    - PC: $3557 ($3879.91)

Blood

Candrielli et al[78]: To investigate the relationships among hydroxyurea adherence, healthcare utilisation and healthcare costs.

- **Design:** Retrospective longitudinal study
- **Follow Up:** 12 months
- **Sample Size:** 312 (A:110, NA:202)
- **Measure:** MPR
- **Classification:** (≥80% = adherent, <80% = nonadherent)
- **Method of Assessment:** Pharmacy claims data
- **Type of Costs:** Adjusted
- **Classification:** All cause and disease state specific
- **Currency Year:** USD, 2008
- **Cost of Nonadherence:**
  - **All cause:**
    - TC: $126996 ($138524.78)
    - IC: $14844 ($16191.55)
    - OC: $101854 ($111100.37)
    - EDC: $734 ($800.63)
    - PC: $3244 ($3538.49)
    - OtPC: $9564 ($10432.23)
To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.

**Design:** retrospective observational study
**Follow Up:** 1527 days
**Sample Size:** 87 (A:21, NA:66)

**Measure:** pharmacy records
**Classification:** (>75% = adherent, ≤75% = nonadherent)
**Method of Assessment:** pharmacy and hospital claims data

**Hospitalization costs**

**Type of Costs:** unadjusted
**Classification:** all cause
**Currency Year:** EUR, 2012

**Cost of Nonadherence**

**All cause:**
HC: €6275.80 ($8893.94)

**Quality:** low
**Classification:** cost outcome description

costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro, DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won

*: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group;
#: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against adherent group; ####: cost per episode of nonadherence


26. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003;11(12):817-22 doi: 10.2165/00115677-200311120-00006 [published Online First: Epub Date].


34. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;49:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]].


### eTable 3: Total cost or total healthcare cost comparison across disease groups

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<tr>
<th>Disease State</th>
<th>Min adj cost per annum per person</th>
<th>Max adj cost per annum per person</th>
<th>Median adj cost per annum per person</th>
<th>Mean adj cost per annum per person</th>
<th>No. adj studies</th>
<th>Min unadj cost per annum per person</th>
<th>Max unadj cost per annum per person</th>
<th>Median unadj cost per annum per person</th>
<th>Mean unadj cost per annum per person</th>
<th>No. unadj studies</th>
<th>Total studies</th>
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<tr>
<td>Cardiovascular Disease</td>
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<td>19472</td>
<td>8080</td>
<td>9204</td>
<td>6</td>
<td>1433</td>
<td>8377.05</td>
<td>5931</td>
<td>4701</td>
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<td>12</td>
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<td>Mental Health</td>
<td>3253</td>
<td>19363</td>
<td>11262</td>
<td>11052</td>
<td>6</td>
<td>2512</td>
<td>25920</td>
<td>17221</td>
<td>16486</td>
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<td>Diabetes Mellitus</td>
<td>2741</td>
<td>9819</td>
<td>6907</td>
<td>6310</td>
<td>7</td>
<td>1142</td>
<td>7950</td>
<td>5534</td>
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<td>Osteoporosis</td>
<td>949</td>
<td>44190</td>
<td>41402</td>
<td>32866</td>
<td>4</td>
<td>669</td>
<td>43404</td>
<td>9921</td>
<td>18190</td>
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<td>Respiratory Disease</td>
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<td>7124</td>
<td>6689</td>
<td>6505</td>
<td>1</td>
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<td>36259</td>
<td>11526</td>
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<td>Gastrointestinal Disease</td>
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<td>37151</td>
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<td>23317</td>
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<td>0</td>
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<td>0</td>
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<td>HIV/AIDS</td>
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<td>16957</td>
<td>30523</td>
<td>23880</td>
<td>3</td>
<td>2015</td>
<td>24322</td>
<td>29406</td>
<td>32872</td>
<td>3</td>
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<td>Parkinson's Disease</td>
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<td>10988</td>
<td>52023</td>
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<td>Musculoskeletal conditions</td>
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<td>3</td>
<td>3408.32</td>
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<td>Cancer</td>
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<td>93637</td>
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<td>2</td>
<td>99638</td>
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<tr>
<td>Addiction</td>
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<td>32872</td>
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<td>Metabolic conditions other than diabetes mellitus</td>
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<td>Blood conditions</td>
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</tbody>
</table>

Total studies: 14

Costs reported in SUS2015 dollars

1 Some studies included both adjusted and unadjusted costs

* Single total cost/total healthcare cost reported

** In addition to disease-specific studies of the economic impact of medication nonadherence, studies reported the all-causes costs, encompassing cost drivers such as comorbidities. Alvarez Paye et al reported all cause costs only.

---

Do not report total cost/total healthcare cost

Single total cost/total healthcare cost reported

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<table>
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<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
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<td></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td></td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
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<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td></td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td></td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td></td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td></td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td></td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td></td>
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<td>Section/topic</td>
<td>#</td>
<td>Checklist item</td>
<td>Reported on page #</td>
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<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
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<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
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<tr>
<td>RESULTS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td></td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
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</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td></td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td></td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td></td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td></td>
</tr>
<tr>
<td>DISCUSSION</td>
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<td></td>
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<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
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<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td></td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
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</tr>
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<td>FUNDING</td>
<td></td>
<td></td>
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<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
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For more information, visit: www.prisma-statement.org.
Economic impact of medication nonadherence by disease groups: a systematic review

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<td>Complete List of Authors</td>
<td>Cutler, Rachelle; University of Technology, Sydney, Australia, Graduate School of Health; Pharmacy Fernandez-Llimos, Fernando; Universidade de Lisboa Instituto de Investigacao do Medicamento, Social Pharmacy Frommer, Michael; University of Sydney Sydney Medical School, Sydney Medical School Benrimoj, Charlie; University of Technology, Sydney, graduate school of health Garcia Cardenas, Victoria; University of Technology, Sydney, Australia, Graduate School of Health; Pharmacy</td>
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<td>Secondary Subject Heading</td>
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Title: Economic impact of medication nonadherence by disease groups: a systematic review

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Word Count:

5961
Abstract

Objective: To determine the economic impact of medication nonadherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in September 2017. Studies quantifying the cost of medication nonadherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy nine individual studies assessing the cost of medication nonadherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of nonadherence per person ranged from $949-$44,190 (in 2015 US dollars). Costs attributed to “all causes” nonadherence ranged from $5,271 to $52,341. Medication possession ratio was the metric most utilized to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of nonadherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication nonadherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication nonadherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardization of the metric measures used to estimate medication nonadherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338
Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication nonadherence via quantifying the cost of medication nonadherence across different disease groups.
- A large comprehensive review – 2,768 citations identified, 79 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.
1 Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources[2]. Medications represent a cost-effective treatment modality[3], but with estimates of 50% nonadherence to long term therapy for chronic illnesses[4], intentional and unintentional medication nonadherence signifies a prevalent and persistent healthcare problem. Medication adherence is defined as ‘the extent to which the patients’ behavior matches agreed recommendations from the prescriber’, emphasizing the importance on the patients’ decisions and highlighting the modifiable aspect of nonadherence[5].

Given the proportion of the population who do not adhere to their medication efforts to improve medication adherence represent an opportunity to enhance health outcomes and health system efficiency. Annual costings of medication nonadherence range from US$100-$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A$7 billion[8 9] in Australia. Additionally ten percent of hospitalizations in older adults are attributed to medication nonadherence [10 11] with the typical nonadherent patient requiring three extra medical visits per year leading to $2000 increased treatment costs per annum[12]. In diabetes the estimated costs savings associated with improving medication nonadherence range from $661 million to $1.16 billion [13]. Nonadherence is thus a critical clinical and economic problem[4].

Healthcare reformers and payers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[14]. However there is still a budgetary problem that needs to be considered, especially given the widespread policy debate over how to best bend the healthcare cost curve downward[15] and the proportion of healthcare budgets spent on prescription medication[16]. Quantifying the cost of medication nonadherence will help demonstrate the causal effect between medication nonadherence, increased disease prevalence and healthcare resource use. Justification of the associated financial benefit may incentivize health policy discussion about the value of medication adherence and promote the adoption of medication adherence intervention programs [15].

The objective of this systematic review was, first, to determine the economic impact of medication nonadherence across multiple disease groups, and second, to review and critically appraise the literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of nonadherence.
2 Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[17].

2.1 Search strategy and selection criteria

A literature search was conducted in September 2017. Studies reporting the cost of medication nonadherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR (“Patient Compliance”[MH] AND (“Drug Therapy”[MH]) OR medication[TIAB]) OR “Medication adherence”[MH] AND (costs[TIAB] OR “Costs and Cost Analysis”[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication nonadherence as a monetary value, ii) systematic reviews, iii) papers not reporting a baseline cost of medication nonadherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RC and VGC) and resolved via consensus.

2.2 Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[18] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardized costs, type of costs, non-cost findings, sub-
group analysis and statistical significance), conclusions and miscellaneous (funding source, references to other relevant studies, limitations and reviewers comments).

Costs were defined as any indicator associated with medication nonadherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients’ families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating-Centre Cost Converter tool [19], allowing meaningful comparisons between nonadherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year utilizing a Gross Domestic Product deflator index and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication nonadherence was derived from the included studies; with nonadherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple nonadherence costs from individual studies may have been included where further sub-classification of nonadherence levels was defined. The analysis assessed nonadherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

2.3 Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [20]. All studies were classified in accordance with Drummond’s distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or
effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RC and VGC).

The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least 75% of Drummond’s criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

2.4 Meta-Analysis

Outcome/indicator costs were independently extracted utilizing predesigned data extraction forms (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs, emergency department costs, and hospitalisation costs) for the purpose of integrating the findings on the cost of medication nonadherence to pool data and increase the power of analysis.
3 Results

3.1 Study Selection

Search strategies retrieved 2768 potential articles after duplicates were removed. Two hundred and eighty nine articles were selected for full text review. Seventy nine studies were included in the review (Figure 1). Numerous other papers do discuss nonadherence costs however addressed tangential issues or did not present primary relevant data. Many studies failed to report the monetary value of medication nonadherence associated with a range of cost estimate indicators.

3.2 Characteristics of individual studies

Sixty-six studies (83%) were conducted in the United States[10 22-86], four in Europe[87-90], four in Asia[91-94], three in Canada[95-97], one in the United Kingdom[98] and one across multiple countries throughout Europe and the United Kingdom[99]. Publication years ranged from 1997 to 2017; in accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used[18] with earlier studies following the same pattern of association between medication nonadherence and increasing healthcare costs. Individual studies reported a large variety of costs, calculated by varying means. Forty-four studies (56%) reported unadjusted costs[22 26 27 30 32-36 38-43 46 48-50 52-56 58 63-68 72 75 81-83 86 88-90 92-94 99], 21 (26%) adjusted costs[10 23-25 29 31 44 51 57 59-61 71 73 76-78 84 85 87 91], 11 a combination of adjusted and unadjusted[28 37 45 47 62 69 70 74 79 80 97], two unadjusted and predicted[95 96] and one predicted costs[98]. The method of determining nonadherence ranged significantly between studies with majority of papers utilizing pharmacy and/or healthcare claims data (97%)[10 22-29 31-52 55 57 59-88 92-97]. Some studies utilized a combination of surveys or questionnaires, observational assessment, previous study data and disease state specific recommended guidelines. Medication possession ratio (MPR) was the most utilized method to calculate patient nonadherence with 51 studies (63%) reporting nonadherence based on this measure[24 25 28 29 32-36 40-44 46 47 49-51 55 57 58 60-64 67-78 81 82 86-88 92-97]; however, the cut-off points to define medication nonadherence differed with some studies classifying nonadherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of nonadherence (11%)[31 37 45 48 52 79 80 83-85], with all other studies utilizing an array of measures including self-report[98], urine testing[56], observational assessment[99], time to discontinuation[59], cumulative possession
ratio[23], disease specific medication management guidelines[66 89], Morisky 4-Item scale[53],
medication gaps[38], prescription refill rates[22 27] and medication supplies[10]. The main
characteristics of the included studies are summarized in eTable 2.

3.3 Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75
87 93], 59 of medium[10 22-26 28-32 34-36 38 39 41-48 53-56 58 59 61-64 66 67 69 70 72 73 76-82
84-86 88 89 91 94-99] and ten of low quality[27 49 60 65 68 74 83 90 92]. Scores ranged from 26.1%
to 87.5% (mean 62.63%). Only one study identified the form of economic evaluation used and
justified it in relation to the questions that were being addressed [71]. The item ‘the choice of
discount rate is stated and justified’ was applicable only to studies covering a time period of more
than one year; all studies that cover more than one year failed to identify or explain why costs had
not been discounted. Details of the analysis and interpretation of results were lacking in the majority
of studies resulting in medium or low quality scores.

Through utilization of Drummond’s distinguishing characteristics of healthcare evaluations
criteria[20] it is apparent that no full economic evaluation was conducted in any of the included
studies. All studies performed partial economic evaluations of varying extents. The classification of
economic evaluations resulted in 59 cost description studies (74% of those included), 15 cost
outcome descriptions and five cost analysis studies (eTable 2).

3.4 Medication nonadherence and costs

The cost analysis of studies (figure 2 and figure 3) reported annual medication nonadherence costs
incurred by the patient per year. The adjusted total cost of nonadherence across all disease groups
ranged from $949 to $52,341, while the unadjusted total cost ranged from $669 to $162,699. Figure
2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by
patients across disease groups where three or more studies were included for review. All cause costs
encompass nonadherence costs incurred in mixed disease state studies, taking into account other
confounding factors such as comorbidities.

Many different indicators were used to estimate medication nonadherence costs with no clear
definition of what was incorporated in each cost component. The composition of included costs to
estimate total cost or total healthcare cost varied significantly between studies thus indicators were
grouped for analysis based on the original studies classification of the cost. The main ones were total cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (46%), medical costs (29%), emergency department costs (27%), and hospitalization costs (18%) (eTable 2). Avoidable costs (e.g., unnecessary hospitalizations, physician office visits and healthcare resource utilization) were not well defined with majority of studies failing to quantify these costs.

Lower levels of adherence across all measures (e.g., MPR, PDC) were generally associated with higher total costs. From those that reported total or total healthcare costs, 39 studies (49%) reported nonadherence costs to be greater than adherence costs [24 25 27 29 31 32 34 37-39 42 43 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported nonadherence costs to be less than adherence costs [23 26 36 44 59 63 66 81 92 94 95]. Four reported fluctuating findings based on varying nonadherence cost subcategories [33 48 67 93] and two studies reported conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total nonadherence costs and lower disease group specific nonadherence costs were reported in four studies [41 68 85 91], whereas Hansen et al [47] reported all cause total nonadherence costs to be lower ($18540 vs. $52302) but disease group specific nonadherence total costs to be higher ($3,879 vs. $2,954).

The association between nonadherence and cost was determined through use of a variety of scaling systems. The most utilized methods were MPR and PDC. These measures could then further be subcategorized based on the percentage of adherence/nonadherence. The 80-100% category was classified as the most adherent group across both scales, with the most common definition of nonadherence being <80% MPR or PDC.

3.5 Cost of medication nonadherence via disease group

Cancer exhibited more than double the cost variation of all other disease groups ($114,101). Osteoporosis ($43,240 vs. $42,734), diabetes mellitus ($7,077 vs. $6,808) and mental health ($16,110 vs. $23,408) cost variations were similar between adjusted and unadjusted costs while cardiovascular disease adjusted costs were more than double unadjusted costs ($16,124 vs. $6,943). Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy and parkinson’s disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal
conditions. Direct costs had greater economic bearing than indirect costs across all disease groups. Cost comparisons across disease groups are summarized in eTable 3.

3.5.1 Cardiovascular Disease

Twelve studies measured the economic impact of medication nonadherence in cardiovascular disease [10 24 31 61 65 67 76 81 93 95 96]. Six studies reported adjusted costs [10 24 31 61 62 76] with annual costs being extrapolated for two of these [31 61]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs [10 31 61 62 76], medical costs [10 24 31 61 76] and outpatient costs [31 62]. The annual economic cost of nonadherence ranged from $3,347 to $19,472. Sokol et al [10] evaluated the economic impact of medication nonadherence across three cardiovascular conditions; hypertension, hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined, pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups.

Total costs and medical costs were lower for the adherent groups of hypertension and hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.

Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total costs of nonadherence ranging from $1,433 to $8,377 [65 67 81 93 95 96]. Rizzo et al [65] reported cost findings through subgroup analysis of five conditions. For all conditions the total healthcare costs were higher for nonadherent groups compared with adherent. While Zhao et al [81], categorized participants into adherence subgroups; finding that total healthcare costs were lower for the nonadherent population. The remaining studies used five key indicators to determine the economic impact: inpatient costs [67 93], outpatient costs [67 93], pharmacy costs [67 95 96], medical costs [95 96] and hospitalization costs [95 96].

3.5.2 Mental Health

The analyses used to report the economic impact of medication nonadherence in mental health varied widely. Eleven of 14 studies provided a total nonadherence cost estimate in mental health [23 25 27 52 59 66 73 82 91 98 99], with annual cost data being extrapolated for four of these [27 66 82 99]. Six studies used adjusted costs, finding that the total annual cost of nonadherence per patient ranged from $3,252 to $19,363 [23 25 59 60 73 91]. Bagalman et al [25] focused primarily on the indirect costs associated with nonadherence – short-term disability, workers compensation and paid time off costs while Robertson et al [82] highlighted the association between medication nonadherence and incarceration, with findings indicating incarceration and arrest costs are higher...
for worsening degrees of nonadherence. All other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication nonadherence were pharmacy costs,[23 39 52 59 60 66 73 99], inpatient costs,[39 60 66 98 99], outpatient costs,[23 39 59 66 99] and hospitalization costs.[22 23 59 99].

The total unadjusted cost for medication nonadherence ranged from $2,512 to $25,920 as reported in four studies.[52 66 82 99]. Becker et al.[27] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%, <25%), nonadherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al.[98] outlined the predicted cost of nonadherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

3.5.3 Diabetes mellitus:

Eleven studies reported a cost measurement of the impact of medication nonadherence with reference to the health system and the individual.[40 45 47 51 74 76 83 84 92 94 97]. One study estimated that the total US cost attributable to nonadherence in diabetes was slightly over $5 billion.[51]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819.[47 51 74 76 84 97]. One study reported total costs in relation to subgroup analysis based on MPR level.[74], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients.[76]. Curtis et al.[84] utilized a diabetic population to report all cause costs, with nonadherence costs being higher than adherence costs across all outcome indicators bar pharmacy costs.

A further four studies reported unadjusted cost findings.[40 83 92 94] with an additional four studies reporting unadjusted costs in in combination with adjusted values.[45 47 74 97]. Unadjusted total healthcare costs and/or total costs ranged from $1,142 to $7,951. Extrapolated annual costs were determined for two studies based on cost data presented.[40 94].

The most prominent indicators used to determine costs were pharmacy costs,[40 45 47 74 76 83 84 97], outpatient costs,[40 47 76 84 94 97], inpatient costs,[47 76 97] and hospitalization costs.[51 92 94]. All studies assessed the direct costs associated with medication nonadherence. One study evaluated the relationship between nonadherence and short term disability costs in addition to assessing direct costs.[45].
3.5.4 Osteoporosis:

The cost of medication nonadherence in relation to osteoporosis was predominately examined through analysis of the direct costs associated with nonadherence using total healthcare costs and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department costs. Two studies further assessed the economic impact of nonadherence through evaluation of fracture related costs [48 88]. Four out of 11 studies reported the adjusted cost of medication nonadherence in addition to reporting unadjusted costs [28 79 80 87]. Three studies further classified nonadherence through subgroup analysis, with Briesacher et al[28] using MPR 20% interval increases and the two studies conducted by Zhao et al[79 80] using PDC, with ≥80% classified as high adherence, 50-79% medium adherence and <50% low adherence. In the studies conducted by Zhao et al[79 80], total healthcare costs were highest for the medium adherence group ($41,402 and $44,190) followed by the highest adherence group ($37,553 and $43,863), and lowest for the low adherence group ($34,019 and $43,771). These annual costs were extrapolated from study data. In contrast, Briesacher et al[28] modelled the subgroup analyses against the lowest adherence group (<20% MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of nonadherence ranged from $669 to $43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In the three studies that reported the lowest level of nonadherence to be PDC <50%, the cost of this category ranged from $16,938 to $43,404 [48 79 80].

One study examined only the medical costs of nonadherence through MPR subgroup analysis in commercial and Medicare supplemental populations. The findings were that, for all levels of nonadherence, costs of nonadherence were higher for Medicare supplemental patients [46].

3.5.5 Respiratory Disease:

The majority of studies reported unadjusted cost of medication nonadherence, with significant variation in the method of adherence classification[36 38 53 64 89]. Two studies used MPR[36 64], one the Morisky 4-Item scale[53], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[89] and one a 37 day gap in claims data[38]. Joshi et al[53] reported on the indirect costs of medication nonadherence through consideration of losses in total productivity costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs. Delea et al[36] reported a direct relationship between decreases in medication nonadherence level and total costs, whereas Quittner et al[64] reported an inverse relationship between decreases in medication nonadherence level and total healthcare cost. The total expenses associated with the
lowest subgroup of adherence across all measures ranged from $804 to $36,259. In contrast Davis et
al[85] utilized adjusted costs across four sub-classifications of PDC adherence ranges to demonstrate
that nonadherence costs were lower than adherence costs in all costing outcomes reported except
hospitalization costs.

3.5.6 Gastrointestinal Disease:

Three of five studies reported the adjusted annual cost of medication nonadherence per patient
utilizing the MPR method [44 57 71]. Of these, two reported the total cost ($12,085 and $37,151)[44
71] with the main contributors to the overall total cost being inpatient costs (22% and 37%),
outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies utilized infusion rates to assess nonadherence with neither reporting the
total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalization costs to be
$42,854 while Kane et al[54] reported a significantly lower cost at $5,566 in addition to other direct
cost contributors.

3.5.7 Epilepsy:

Three studies reported the economic impact of medication nonadherence in epilepsy. All reported
unadjusted costs using an MPR cut off of <80%[35 42 43]. The main economic indicators used to
assess total costs were inpatient costs ($2,289 to $6,874), emergency department visit costs ($331
to $669) and pharmacy costs ($442 to $1,067). Davis et al[35] modelled the costs of the
nonadherent group against the adherent group. The annual costs reported by Faught et al[43] were
extrapolated from original cost data. The total cost of nonadherence in epilepsy ranged from $1,866
to $22,673.

3.5.8 HIV/AIDS:

The economic impact of medication nonadherence for HIV and AIDS patients reported amongst all
three studies was similar [26 32 63]. Two of the three studies examined the costs only for HIV[26
32], while Pruitt et al[63] assessed the cost in AIDS as well as HIV. The total unadjusted costs for
nonadherent HIV patients ranged from $16,957 to $30,068 with one study further categorizing
patients with HIV as having either a high viral load or low viral load[26]. The total cost of
nonadherence in AIDS was $30,523[63]. All studies used comparable indicators (total cost, inpatient
cost, outpatient cost, pharmacy cost) to determine the cost of nonadherence.
3.5.9 Parkinson’s Disease:

The direct costs associated with Parkinson’s disease were assessed in all three studies. The unadjusted total cost ranged from $10,988 to $52,023 [34 37 72]. Wei et al[72] further sub-grouped patients into MPR adherence percentage categories, and found that costs increased in all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with nonadherence. One study additionally reported the adjusted cost, estimating that $10,290 could be attributed to medication nonadherence annually[37].

3.5.10 Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication nonadherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of nonadherence[50], one assessed only the medical costs[69] and one examined the direct costs in commercial and Medicare supplemental patient populations[78]. Zhao et al[78] reported the adjusted annual cost in the commercial population to be $22,609, and in the Medicare supplemental group, $28,126. Ivanova et al[50] reported only unadjusted costs and the annual total cost of $3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of nonadherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

3.5.11 Cancer:

Two studies evaluated the effects of medication nonadherence in cancer[33 75]. One study reported total annual costs of $119,416[75], while the other gave a subgroup analysis based on classified adherence levels[33]. In general the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs ($162,699 and $67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

3.5.12 Addiction:

The adjusted annual total healthcare cost of medication nonadherence was reported as $53,504[56] while the unadjusted cost ranged from $16,996 to $52,213 [56 70 86]. Leider et al[56] reported the main contributors to this cost to be outpatient costs ($10,829) and pharmacy costs ($8,855), whereas Tkacz et al[70] and Ruetsch et al[86] reported them to be inpatient costs ($28,407 and $5,808) and outpatient costs ($15,460 and $5,743).
3.5.13 Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication nonadherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of $138,525[55]. The economic indicators used to derive this cost were inpatient costs ($16,192), outpatient costs ($111,100), emergency department visit costs ($801) and pharmacy costs ($3,538).

3.5.14 Blood conditions:

Candrilli et al[29] reported cost findings on the relationship between nonadherence and healthcare costs, giving an adjusted total cost estimate of $13,458 for nonadherence classified as MPR <80%.

3.5.15 All causes:

In addition to disease-specific studies of the economic impact of medication nonadherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[47 50 61 64 66 85 99]. Eleven studies reported on economic indicators without giving total cost or total healthcare cost[22 45 46 54 55 57 60 81 83 90 99], and one study reported on costs per episode of nonadherence[90]. The adjusted cost of medication nonadherence was reported in 14 studies with an estimated range of $5,271 to $52,341 [10 29 31 57 59-61 71 76 77 84 85 87 91]. Sokol et al[10] reported the all-cause cost of nonadherence through subgroup analysis of disease states and MPR levels, while Pittman et al[61] reported only using MPR level breakdown.

Fifteen studies reported the unadjusted economic impact of medication nonadherence with an estimated range of $1,037 to $53,793 [22 41 46 50 54 55 58 64-66 68 81 83 90 99]. A further four studies reported adjusted and unadjusted costs[37 45 47 97]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).
3.6 Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication nonadherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of required statistical parameters in particular standard deviation[100]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.
4 Discussion

This systemic review broadens the scope of knowledge associated with the economic impact of medication nonadherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication nonadherence. Medication nonadherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, emergency department costs, medical costs and hospitalization costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with nonadherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of nonadherence, but no research has attempted to synthesize costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. parkinsons disease). Similarly there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of nonadherence behavior and associated costs is required to adequately quantify the overall cost of nonadherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication nonadherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to nonadherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritization of healthcare interventions to address medication nonadherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication nonadherence facilitates the extrapolation of annual national cost estimates attributable to
medication nonadherence thus enabling greater planning in terms of health policy to help counteract increasing avoidable costs.

The economic, clinical and humanistic consequences of medication nonadherence will continue to grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to adequately address the determinants of adherence through utilization of effective health interventions. Haynes et al [101] highlights that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments”. Improving medication adherence provides an opportunity for major cost savings to healthcare systems. Predictions of population health outcomes through utilization of treatment efficacy data need to be used in conjunction with adherence rates to inform planning and project evaluation[4]. The correlation between increased nonadherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [102], who compared six key adherence measures on the same study participants, found that the measures produced similar adherence values for all participants, although PDC and continuous measure of medication gaps produced slightly lower values. While this highlights the comparability of the measures of medication nonadherence, it further justifies the need to agree on consistent methods for estimating nonadherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication nonadherence. MPR was used in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with those found recently by Sattler et al [103]. Even though the measures of medication nonadherence may be comparable, the definition of MPR and the cut-off points to define nonadherence differed significantly. Dragomir et al[95] defined MPR as the total days’ supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalization; Wu et al[76] removed the number of hospitalized days from the calculation; and Pittman et al[61] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Nonadherence could also be further classified into subcategories within MPR and PDC based on percentages. Thirty studies defined nonadherence as MPR< 80%, and 12 studies categorized nonadherence into varying percentage subgroups. While Karve et al[104] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent
hospitalizations in patients across a broad array of chronic diseases, 76 of the 79 studies included in this review examined more than just hospitalization costs as an indicator metric. Further research is required to identify and standardize nonadherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 79 studies covered, 35 different indicators were used to measure the cost of nonadherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardized approach be established to measure and report the economic impact of medication nonadherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of nonadherence cost that is attributable to each outcome to determine an appropriate model[105].

The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalization costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of nonadherence be undertaken to help develop a tool that can be utilized for future research.

Many studies have examined the relationship between nonadherence and economic outcomes using a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

Economic evaluations inform decisions on how to best make use of scarce societal health resources through offering an organized consideration of the range of possible alternative courses of action and the evidence of the likely effects of each[20]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication nonadherence. Pharmacy claims data were utilized by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with nonadherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasized the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106]
highlighted the need for more information on the consequences of nonadherence, so that economic
evaluations could reflect the potential long-term effect of this growing problem.

Of the seventy nine included studies, sixty six of the studies were conducted in the United States.
Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and
disease groups. Comparison of costs between healthcare systems is difficult as no two are the same
and as healthcare is generally more expensive in the United States cost estimates may not reflect
average values. Thus caution needs to be taken when interpreting results however findings help to
represent the significance of the economic burden medication nonadherence plays. Analysis of
studies not conducted in the United States support the finding that generally medication
nonadherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication nonadherence, the
inclusion of studies undertaken in the late 1990s and early 2000s may have affected the
comparability of results, despite the fact that these studies met the inclusion criteria[22 23 65 73 74
98]. The quality of data presents a limitation. Information on disease groups with fewer included
studies may be less reliable than information on those with more. However, our findings affirm the
pattern of association between nonadherence and increasing healthcare costs.
5 Conclusion

Medication nonadherence places a significant cost burden on healthcare systems. However, differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the nonadherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Utilization of existing data could help to better define costs and provide valuable input into the development of an economic framework to standardize the economic impact of medication nonadherence.
6 Footnotes

Contributors: RC, VGC, SB, FFL and MF conceived the paper. RC and VGC performed all the data extraction and quality assessment. RC drafted the initial form and all revisions of this manuscript. All other authors (RC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

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Figure Legends

Figure 1: PRISMA Flow Diagram
The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2768 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication nonadherence using original cost data. Intervention studies were required to report baseline data. Seventy nine original studies met the inclusion criteria.

Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year
Encompass the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Figure 1: Annual Unadjusted Medication Nonadherence Costs per patient per year
Encompass the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy and addiction only included three studies limiting the range of costs. All cause costs encompass nonadherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.
Figure 1: Flow diagram of references identified, retrieved and included in the systematic review

209x297mm (300 x 300 DPI)
Figure 2: Annual Adjusted Medication Nonadherence Costs per patient per year

*Disease groups with three or more studies were included. Gastrointestinal only included three studies limiting the range of costs.

** All cause costs: mixed disease state studies

209x297mm (300 x 300 DPI)
Figure 3: Annual Unadjusted Medication Nonadherence Costs per patient per year

*Disease groups with three or more studies were included. Epilepsy and Addiction only included three studies limiting the range of costs.

** All cause costs: mixed disease state studies

209x297mm (300 x 300 DPI)
eTable 1 Search Strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopus</td>
<td>( TITLE-ABS-KEY ( medication AND compliance OR patient AND compliance ) ) AND ( TITLE-ABS-KEY ( statistical AND model ) ) AND ( TITLE-ABS-KEY ( health AND care AND cost ) )</td>
</tr>
</tbody>
</table>

1 In accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used.
### eTable 2: Studies identified with costs reported by adherence level and disease group

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Objective</th>
<th>Study Characteristics</th>
<th>Adherence (as reported in paper)</th>
<th>Outcomes/Indicators</th>
<th>Results (USD, 2015)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Dragomir et al[4] 2010 Canada

**To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalization costs.**

**Design:** Retrospective cohort study  
**Follow Up:** 3 years  
**Sample Size:** 56,896 (A:38,217, NA:18,679)

**Measure:** MPR  
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent  
**Method of Assessment:** pharmacy claims data

**Total Healthcare Costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Unadjusted and Predicted Disease State Specific and Hospitalized Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification:</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Cost of Nonadherence:** Unadjusted Disease State Specific: THC: $7,165 ($6,900.87), PC: $1,800 ($1,733.64), MC: $1,370 ($1,319.50), HC: $3,995 ($3,847.73)  
| **Unadjusted Hospitalized Patients:** THC: $17,397 ($16,755.67), PC: $2,685 ($2,586.02), MC: $2,608 ($2,511.86), HC: $12,108 ($11,657.79)  
| **Predicted Disease State Specific:** HC: $3,877 ($3,734.08)  
| **Predicted Hospitalized Patient:** HC: $11,715 ($11,283.13) |

**Quality:** medium  
**Classification:** cost description

---

### Dragomir et al[5] 2010 Canada

**To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.**

**Design:** Retrospective cohort study  
**Follow Up:** 3 years  
**Sample Size:** 55,134 (A:28,549, NA:26,585)

**Measure:** MPR  
**Classification:** MPR≥80 = adherent, MPR < 80 = nonadherent  
**Method of Assessment:** pharmacy claims data

**Total Healthcare Costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Unadjusted and Predicted Disease State Specific and Hospitalized Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification:</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Cost of Nonadherence:** Unadjusted Disease State Specific: THC: $6,243 ($6,175.76), PC: $2,506 ($2,479.01), MC: $1,241 ($1,227.63), HC: $2,496 ($2,469.12)  
| **Unadjusted Hospitalized Patients:** THC: $14,738 ($14,566.40), PC: $3,374 ($3,337.66), MC: $2,475 ($2,448.34), HC: $8,876 ($8,780.40)  
| **Predicted Disease State Specific:** |

**Quality:** medium  
**Classification:** cost description
To examine the relation among statin adherence, subsequent hospitalizations and healthcare costs.

Design: Retrospective cohort study
Follow Up: 18 months

Measure: MPR
Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence

Method of Assessment: pharmacy claims data

Total Healthcare Costs
Type of Costs: adjusted
Classification: all cause and disease state specific
Currency Year: USD, 2009
Cost of Nonadherence: all cause:
THC(>80):$6798.67 ($7505.66),
THC(60-79):$7072.67 ($7808.16),
THC(<59):$401.33 ($8170.99),
PC(>80):$1767.33 ($1951.11),
PC(60-79):$1789.33 ($1975.40),
PC(<59):$1937.33 ($2138.79),
MC(>80):$4472.67 ($4937.78),
MC(60-79):$4840.67 ($5344.05,
MC(<59):$5138.67 ($5673.04)

Disease state specific:
PC(>80):$558.67 ($616.77),
PC(60-79):$442.67 ($488.70),
PC(<59):$25.33 ($359.16),
MC(>80):$1596.67 ($1762.71),
MC(60-79):$1722 ($1901.07),
MC(<59):$1792.67 ($1979.09)

Quality: medium
Classification: cost description

To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalizations, emergency department visits and

Design: Retrospective cohort study
Follow Up: 2 years

Measure: MPR
Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence: Adjusted:
THC(>80):$7261 ($8077.79),
THC(60-79):$7530 ($8377.05),
THC(<59):$9370 ($8199.05),
OC(>80):$3390 ($3771.34),
OC(60-79):$3705 ($4121.77),
OC(<59):$325.33 ($359.16),

Quality: medium
Classification: cost description
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>To investigate variations in compliance with four classes of antihypertensive agents - diuretics, ACEIs, CCBs and β-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Design:** Retrospective cohort study
**Follow Up:** 12 months
**Sample Size:** 7211(P:2668, NC:3101, NP:649, T:793)

**Measure:** ordinary least square regression analysis
**Classification:**
- >80% = persistent
- ≥30<80% = non-compliance
- <30%

**Total Healthcare Costs**

<table>
<thead>
<tr>
<th>Type of Costs:</th>
<th>Unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC(&gt;80):</td>
<td>$7182 ($7989.90),</td>
</tr>
<tr>
<td>THC(60-79):</td>
<td>$7560 ($8410.42),</td>
</tr>
<tr>
<td>THC(&lt;59):</td>
<td>$7995 ($8894.35),</td>
</tr>
<tr>
<td>OC(&gt;80):</td>
<td>$3396 ($3778.01),</td>
</tr>
<tr>
<td>OC(60-79):</td>
<td>$3635 ($4043.90),</td>
</tr>
<tr>
<td>OC(&lt;59):</td>
<td>$3887 ($4324.25),</td>
</tr>
<tr>
<td>EDC(&gt;80):</td>
<td>$101 ($113.47),</td>
</tr>
<tr>
<td>EDC(60-79):</td>
<td>$131 ($145.74),</td>
</tr>
<tr>
<td>EDC(&lt;59):</td>
<td>$172 ($191.35),</td>
</tr>
<tr>
<td>PC(&gt;80):</td>
<td>$2317 ($2577.64),</td>
</tr>
<tr>
<td>PC(60-79):</td>
<td>$2034 ($2262.80),</td>
</tr>
<tr>
<td>PC(&lt;59):</td>
<td>$1880 ($2091.48),</td>
</tr>
<tr>
<td>HC(&gt;80):</td>
<td>$1366 ($1519.66),</td>
</tr>
<tr>
<td>HC(60-79):</td>
<td>$1759 ($1956.87),</td>
</tr>
<tr>
<td>HC(&lt;59):</td>
<td>$2057 ($2288.39),</td>
</tr>
</tbody>
</table>

**Quality:** low

**Classification:** cost description

**Currency Year:** USD, 1994

**Cost of Nonadherence:**
- All cause:
  - THC(>80): $102 ($113.47),
  - THC(60-79): $131 ($145.74),
  - THC(<59): $172 ($191.35),
  - PC(>80): $2317 ($2577.64),
  - PC(60-79): $2034 ($2262.80),
  - PC(<59): $1880 ($2091.48),
  - HC(>80): $1366 ($1519.66),
  - HC(60-79): $1759 ($1956.87),
  - HC(<59): $2057 ($2288.39),
blockers and the health care costs associated with various degrees of compliance.

Method of Assessment: pharmacy claims data

<table>
<thead>
<tr>
<th>Disease state specific</th>
<th>THC(&lt;30)</th>
<th>($735) ($1098.53)</th>
</tr>
</thead>
</table>
| Renal: THC(>80) | $2135 ($3190.98), THC(30-80) | $2488 ($3718.58), THC(<30) | $2529 ($3779.86), Acute MI: THC(>80) | $1358 ($2029.67), THC(30-80) | $1711 ($2557.27), THCHC(<30) | $1752 ($2618.55), Diabetes: THC(>80) | $770 ($1150.85), THC(30-80) | $1123 ($1678.44), THC(<30) | $1164 ($1739.72), CHF: THC(>80) | $698 ($1043.23), THC(30-80) | $1051 ($1570.83), THC(<30) | $1092 ($1632.11), Angina: THC(>80) | $702 ($1049.21), THC(30-80) | $1055 ($1576.81), THC(<30) | $1096 ($1638.09), Type of costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 1998 Cost of Nonadherence: All cause: Diabetes: TC(1-19) | $16498 ($23071.58), TC(20-39) | $13077 ($18287.49), TC(40-59) | $12978 ($18149.05), TC(60-79) | $11484 ($16059.77), TC(80-100) | $8886 ($12426.60), PC(1-19) | $3512 ($1834.76), Quality: medium Classification: cost description

To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Design: Retrospective cohort observational study
Follow Up: 12 months
Sample Size: 137277
Method of Assessment: pharmacy claims data

<table>
<thead>
<tr>
<th>Condition</th>
<th>Range</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension:</td>
<td></td>
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</tbody>
</table>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

| PC (40-59) | $1247 ($1743.86) |
| PC (60-79) | $1736 ($2427.70) |
| PC (80-100) | $1972 ($2757.74) |
| MC (1-19) | $39849 ($13773.30) |
| MC (20-39) | $66830 ($9551.39) |
| MC (40-59) | $5509 ($7704.04) |
| MC (60-79) | $6676 ($9336.03) |
| MC (80-100) | $4780 ($6684.58) |
| CHF: | |
| TC (1-19) | $23964 ($33512.38) |
| TC (20-39) | $19188 ($26833.40) |
| TC (40-59) | $26311 ($36794.54) |
| TC (60-79) | $29785 ($41652.74) |
| TC (80-100) | $22164 ($30995.18) |
| PC (1-19) | $1961 ($2742.35) |
| PC (20-39) | $2055 ($2873.81) |
| PC (40-59) | $2208 ($3087.77) |
| MC (1-19) | $22003 ($30770.03) |
| MC (20-39) | $17133 ($23959.59) |
| MC (40-59) | $24103 ($33706.77) |
| MC (60-79) | $26373 ($36881.24) |
| MC (80-100) | $19056 ($26648.81) |

Disease state specific: Diabetes:
<p>| TC (1-19) | $8867 ($12400.03) |
| TC (20-39) | $7124 ($9916.90) |
| TC (40-59) | $5522 ($9120.67) |
| TC (60-79) | $6291 ($8797.63) |
| TC (80-100) | $4570 ($6390.90) |
| PC (1-19) | $85 ($76.91) |
| PC (20-39) | $165 ($230.74) |
| PC (40-59) | $285 ($398.56) |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Age Group 1</th>
<th>Age Group 2</th>
<th>Age Group 3</th>
<th>Age Group 4</th>
<th>Age Group 5</th>
<th>Age Group 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC(80-100): $483 ($6129.39),</td>
<td>MC(40-59): $5113 ($7150.26),</td>
<td>MC(60-79): $4977 ($6960.07),</td>
<td>Hypercholesterolemia:</td>
<td>MC(80-100): $5438 ($6129.39),</td>
<td>Mc(80-100): $53808 ($5325.29),</td>
</tr>
<tr>
<td></td>
<td>MC(1-19): $5888 ($9632.50),</td>
<td>TC(20-39): $4999 ($6990.84),</td>
<td>TC(40-59): $5349.06),</td>
<td>TC(60-79): $5451 ($7748.79),</td>
<td>TC(80-100): $3924 ($5487.51),</td>
<td>PC(1-19): $38 ($109.08),</td>
</tr>
<tr>
<td></td>
<td>MC(1-19): $8812 ($12323.11),</td>
<td>MC(20-39): $6959 ($9731.79),</td>
<td>MC(40-59): $6237 ($8722.11),</td>
<td>MC(60-79): $5887 ($8232.66),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
</tr>
<tr>
<td></td>
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<td>MC(20-39): $6237 ($8722.11),</td>
<td>MC(40-59): $6237 ($8722.11),</td>
<td>MC(60-79): $5887 ($8232.66),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
</tr>
<tr>
<td>Hypercholesterolemia:</td>
<td>TC(1-19): $8812 ($12323.11),</td>
<td>TC(20-39): $6959 ($9731.79),</td>
<td>TC(40-59): $6237 ($8722.11),</td>
<td>TC(60-79): $5887 ($8232.66),</td>
<td>TC(80-100): $53808 ($5325.29),</td>
<td>PC(1-19): $31 ($43.35),</td>
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<td></td>
<td>MC(1-19): $8812 ($12323.11),</td>
<td>MC(20-39): $6959 ($9731.79),</td>
<td>MC(40-59): $6237 ($8722.11),</td>
<td>MC(60-79): $5887 ($8232.66),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
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<td>MC(1-19): $8812 ($12323.11),</td>
<td>MC(20-39): $6959 ($9731.79),</td>
<td>MC(40-59): $6237 ($8722.11),</td>
<td>MC(60-79): $5887 ($8232.66),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
<td>MC(80-100): $53808 ($5325.29),</td>
</tr>
</tbody>
</table>
To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patient with complicated and uncomplicated hypertension and to assess:

**Design:** Retrospective cohort study

**Follow Up:** 3.3 years

**Sample Size:** 15206 (not specified)

**Measure:** MPR

**Classification:**
- MPR<80 = undersupply
- MPR>120 = oversupply

**Method of Assessment:** pharmacy claims data

**Total Healthcare Costs**
- Inpatient Costs
- Outpatient Costs
- Pharmacy Costs

**Type of Costs:** unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2002

**Cost of Nonadherence:**
- THC:$6032.5 ($7830.11), IC:$2067 ($2682.94), OC:$3965 ($5146.52), PC:$130 ($168.74)

**Quality:** medium

**Classification:** cost description
examine the association of refill adherence with hospitalization and healthcare costs among these patients.

**Wu et al[11]**

2011  
US  
To study statin adherence and assess associated medical utilisation and healthcare costs in patients with type 2 diabetes, based on national Medicaid database.  
**Design:** Retrospective cohort study  
**Follow Up:** 1 year  
**Sample Size:** 1705 (A:624, NA:1081)  
**Measure:** MPR  
**Classification:** MPR≥80 = adherent, MPR <80 = nonadherent  
**Method of Assessment:** pharmacy claims data  
**Total Healthcare Costs**  
**Pharmacy Costs**  
**Medical Costs**  
**Type of Costs:** adjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 2005  
**Cost of Nonadherence:** all cause: THC:$17807 ($21370.30), PC:$4915 ($5898.52), MC:$12892 ($15471.77)  
Disease state specific: THC:$2789 ($3347.10), PC:$489 ($586.85), MC:$2300 ($2760.25)  
**Quality:** medium  
**Classification:** cost description

**Zhao et al[12]**

2014  
US  
To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.  
**Design:** Retrospective cohort study  
**Follow Up:** 1 year  
**Sample Size:** 10312  
**Measure:** MPR  
**Classification:** <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100%  
**Method of Assessment:** pharmacy claims data, census data  
**Total Healthcare Costs**  
**Pharmacy Costs**  
**Medical Costs**  
**Type of Costs:** unadjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 2010  
**Cost of Nonadherence:** all cause: PC(96-100):$2976.80 ($3247.04), PC(90-95):$2826.99 ($3083.63), PC(85-89):$2795.39 ($3049.16), PC(80-84):$2690.89 ($2935.17), PC(70-79):$2192.83 ($2391.90), PC(60-69):$2323.27 ($2534.18), PC(40-59):$2153.93 ($2349.47), PC(<40):$1749.18 ($1907.97)  
Disease state specific: THC(96-100):$6536.05 ($7129.40), THC(90-95):$6493.80 ($7083.31), THC(85-89):$6459.40 ($7045.79),
Mental Health

Bagalman et al[13]
2010
US
To examine the association between treatment adherence and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.

Design: Retrospective cohort study
Follow Up: 1 year
Sample Size: 1258 (A:444, NA:814)

Measure: MPR
Classification: MPR≥80 = adherent, MPR <80 = nonadherent
Method of Assessment: pharmacy claims data

Total Costs
Type of Costs: adjusted
Classification: disease state specific
Currency Year: USD, 2005
Cost of Nonadherence: TC:$6894 ($8273.53), STDC:$2134 ($2561.03), WCC:$762.56 ($914.48), PTOC:$3998 ($4798.03)

Quality: medium
Classification: cost description

Becker et al[14]
Examine treatment

Design: Retrospective

Total Costs
Type of Costs: unadjusted
Quality: low
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Classification</th>
<th>Cost of Nonadherence</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>US</td>
<td>Cohort study</td>
<td>2 years</td>
<td>10330</td>
<td>75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, &lt;25% = negligible adherence</td>
<td>TC(75-100): $13564 ($15792.91), TC(50-74): $13772 ($16035.09), TC(25-49): $15792 ($18387.03), TC(&lt;25): $16156 ($18810.84)</td>
<td>Unadjusted</td>
<td>USD, 2006</td>
<td>Medium</td>
</tr>
<tr>
<td>2005</td>
<td>US</td>
<td>Retrospective database analysis</td>
<td>1 year</td>
<td>7864 (&lt;80%:2655, 80-125%:5065, &gt;125%:144)</td>
<td>&lt;80% = partially compliant, 80-125% = compliant, &gt;125% = overly compliant</td>
<td>IC:$3780 ($4906.39), OC:$504 ($654.19), PC:$1872 ($2429.83), MC:$6228 ($8083.86), POC:$1944 ($2523.29)</td>
<td>Adjusted</td>
<td>USD, 2002</td>
<td>Medium</td>
</tr>
<tr>
<td>2004</td>
<td>US</td>
<td>Retrospective database analysis</td>
<td>1 year</td>
<td>8034 (&lt;80%:2635, 80-100%:4410, &gt;100%:489)</td>
<td>&lt;80% = partially compliant, 80-100% = compliant, &gt;100% = overly compliant</td>
<td>Total costs</td>
<td>Adjusted</td>
<td>USD, 1999</td>
<td>Medium</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
<td>Classification</td>
<td>Type of Costs</td>
<td>Cost of Nonadherence</td>
<td>Quality</td>
<td>Classification</td>
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</tr>
<tr>
<td>Hong et al [17]</td>
<td>Prospective observational study</td>
<td>21 months</td>
<td>1341(A:1024, NA:317)</td>
<td>adherent vs. nonadherent</td>
<td>all cause and disease state specific</td>
<td>GBP, 2008</td>
<td>PC:£55.43 ($94.47)</td>
<td>medium</td>
<td>cost description</td>
</tr>
<tr>
<td>Jiang et al [18]</td>
<td>Retrospective cohort study</td>
<td>2 years</td>
<td>32374(A:11642, NA:20732)</td>
<td>PDC≥80% = adherent, PDC&lt;80% = nonadherent</td>
<td>disease state specific</td>
<td>USD, 2011</td>
<td>PC:$3971 ($4076.69), MSC:$10170 ($10440.68)</td>
<td>low</td>
<td>cost description</td>
</tr>
<tr>
<td><strong>To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.</strong></td>
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</tr>
<tr>
<td><strong>Design:</strong> Retrospective cohort study</td>
<td></td>
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<tr>
<td><strong>Follow Up:</strong> 1 year</td>
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<tr>
<td><strong>Sample Size:</strong> 7848 (A:2774, NA:2774, P:1956, NP:1956)</td>
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<tr>
<td><strong>Measure:</strong> percentage of days of psychiatric prescription (PDP)</td>
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<tr>
<td><strong>Classification:</strong> PDP≥80% = adherent, PDP&lt;80% = nonadherent; persistent = continued medication without interruption ≥ 56 days, non-persistent = at least one medication interruption &gt; 56 days</td>
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<tr>
<td><strong>Method of Assessment:</strong> health insurance data</td>
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<tr>
<td><strong>Type of Costs:</strong> adjusted</td>
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<tr>
<td><strong>Classification:</strong> all cause and disease state specific</td>
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<tr>
<td><strong>Currency Year:</strong> USD, 2011</td>
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<tr>
<td><strong>Cost of Nonadherence:</strong> all cause: TC:$4961 ($5271.40)</td>
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<tr>
<td>Disease state specific: TC:$3061 ($3252.50)</td>
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<td><strong>Quality:</strong> medium</td>
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<tr>
<td><strong>Classification:</strong> cost outcome description</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>To assess the relative impact of non-adherence and other factors associated with resource use and costs incurred by people with schizophrenia.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design:</strong> Retrospective cohort study</td>
</tr>
<tr>
<td><strong>Follow Up:</strong> 1 year</td>
</tr>
<tr>
<td><strong>Sample Size:</strong> 658 (A:549, NA:109)</td>
</tr>
<tr>
<td><strong>Measure:</strong> self-report</td>
</tr>
<tr>
<td><strong>Classification:</strong> adherent vs. nonadherent</td>
</tr>
<tr>
<td><strong>Method of Assessment:</strong> health insurance data</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
</tr>
<tr>
<td><strong>Type of Costs:</strong> predicted</td>
</tr>
<tr>
<td><strong>Classification:</strong> disease state specific</td>
</tr>
<tr>
<td><strong>Currency Year:</strong> GBP, 2001</td>
</tr>
<tr>
<td><strong>Cost of Nonadherence:</strong> TC:£57580 ($116434.12)</td>
</tr>
<tr>
<td>IC:£6714 ($13576.57), ESC:£1603 ($3241.47)</td>
</tr>
<tr>
<td><strong>Quality:</strong> medium</td>
</tr>
<tr>
<td><strong>Classification:</strong> cost analysis</td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td><strong>Offord et al[21]</strong>&lt;br&gt;2013&lt;br&gt;US</td>
</tr>
<tr>
<td>Follow Up: 1 year&lt;br&gt;Sample Size: 1462 (A:589, NA:873)</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Measure</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Offord et al[22]</strong>&lt;br&gt;2013&lt;br&gt;US</td>
<td>Retrospective cohort study</td>
<td>MPR</td>
<td>Inpatient costs</td>
<td>adjusted</td>
<td>low</td>
</tr>
<tr>
<td>Follow Up: 1 year&lt;br&gt;Sample Size: 354 (A:126, NA:228)</td>
<td>Classification: MPR ≥ 70= high adherence, MPR &lt; 70 = low adherence</td>
<td>Pharmacy costs</td>
<td></td>
<td>all cause and disease state specific</td>
<td>cost description</td>
</tr>
<tr>
<td></td>
<td>Method of Assessment: pharmacy claims data</td>
<td></td>
<td></td>
<td>Currency Year: USD, 2008</td>
<td></td>
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<td></td>
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<td></td>
<td>Cost of Nonadherence: all cause:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IC:$9053 ($10071.37),</td>
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<td></td>
<td></td>
<td>PC:$4267 ($4746.99),</td>
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<td>Disease state specific:</td>
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<td></td>
<td>IC:$2468 ($2745.62),</td>
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<td>PC:$1085 ($1207.05)</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Measure</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Robertson et al[23]</strong>&lt;br&gt;2014&lt;br&gt;US</td>
<td>Retrospective cohort study</td>
<td>MPR</td>
<td>Total costs</td>
<td>unadjusted</td>
<td>medium</td>
</tr>
<tr>
<td>Follow Up: 90 days&lt;br&gt;Sample Size: 1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)</td>
<td>Classification: MPR ≥80% = adherent</td>
<td>Inpatient costs</td>
<td>Emergency department costs</td>
<td>disease state specific</td>
<td>cost description</td>
</tr>
<tr>
<td></td>
<td>Method of Assessment: Medicaid claims data</td>
<td>Outpatient costs</td>
<td>Pharmacy costs</td>
<td>Currency Year: USD, 2005</td>
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<td>Cost of Nonadherence*:</td>
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<td></td>
<td>TC(90/90):$28068 ($33495.65),</td>
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<td>TC(60/90):$21720 ($25920.11),</td>
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<td>TC(30/90):$21084 ($25161.12),</td>
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<td>TC(0/90):$2516 ($14936.28),</td>
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<tr>
<td>Type of Costs</td>
<td>IC(90/90)</td>
<td>IC(60/90)</td>
<td>IC(30/90)</td>
<td>IC(0/90)</td>
<td>OC(90/90)</td>
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<tr>
<td>Costs</td>
<td>$12168</td>
<td>$10068</td>
<td>$11376</td>
<td>$592</td>
<td>$6468</td>
</tr>
<tr>
<td>Total costs</td>
<td>$14520.99</td>
<td>$12014.90</td>
<td>$13575.84</td>
<td>$6673.35</td>
<td>$7718.75</td>
</tr>
</tbody>
</table>

*Robinson et al*[24] To determine if the

<p>| Design: Retrospective | Measure: Total costs | Type of Costs: unadjusted | Quality: medium |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Study Title</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
<th>Cost Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>US</td>
<td>Type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed patients.</td>
<td>Claims analysis</td>
<td>6 months</td>
<td>60386 (A:11526, NA:8860)</td>
<td>Antidepressant medication management measures</td>
<td>Meeting less than &lt;3 medication management measures = nonadherent</td>
<td>Inpatient costs</td>
<td>Outpatient costs</td>
<td>ED visit costs Pharmacy costs Physician office visit costs</td>
<td>Classification: all cause and disease state specific</td>
<td>Cost of Nonadherence: all cause: TC:$12658 ($15678.21) IC:$3006 ($3723.24), OC:$6118 ($7577.76), EDC:$334 ($413.69) PC:$3200 ($3963.52), POC:$178 ($220.47) Disease state specific: TC:$2028 ($2511.88) IC:$102 ($126.34), OC:$734 ($809.13), EDC:$18 ($22.29) PC:$1174 ($1454.12), POC:$120 ($148.63)</td>
<td>Classification: cost description</td>
</tr>
<tr>
<td>2003</td>
<td>US</td>
<td>To evaluate the economic impact of antidepressant</td>
<td>Design: Retrospective database analysis</td>
<td>6 months</td>
<td></td>
<td>Measure: MPR</td>
<td>Classification: MPR≥70% = Total costs Pharmacy costs</td>
<td>Type of Costs: adjusted</td>
<td>Classification: disease state specific</td>
<td>Currency Year: USD, 1999</td>
<td>Classification: cost description</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Follow Up</td>
<td>Sample Size</td>
<td>Measure</td>
<td>Classification</td>
<td>Total costs</td>
<td>Type of Costs</td>
<td>Currency Year</td>
<td>Quality</td>
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<tr>
<td>Diabetes&lt;br&gt;&lt;br&gt; <em>An et al</em> [27]&lt;br&gt;2014&lt;br&gt;Korea</td>
<td>Prospective cohort study&lt;br&gt;Follow Up: 3 years&lt;br&gt;Sample Size: 608 (A:472, NA:136)</td>
<td>MPR&lt;br&gt;MPR&lt;90% = nonadherent&lt;br&gt;MPR≥90% = adherent</td>
<td>Total costs&lt;br&gt;Outpatient costs&lt;br&gt;Hospitalization costs</td>
<td>unadjusted&lt;br&gt;disease state specific</td>
<td>USD, 2007</td>
<td>medium</td>
<td>$11815 ($16290.09)&lt;br&gt;$1123 ($1548.35)&lt;br&gt;$10692 ($14741.74)</td>
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<tr>
<td>Buysman et al [28]&lt;br&gt;2017&lt;br&gt;US</td>
<td>Retrospective database analysis&lt;br&gt;Follow Up: 12 months&lt;br&gt;Sample Size: 2261 (A:1215, NA:1046)</td>
<td>PDC&lt;br&gt;PDC80% = highly adherent,&lt;br&gt;PDC&lt;80% = less than highly adherent</td>
<td>Pharmacy costs</td>
<td>unadjusted&lt;br&gt;all cause and disease state specific</td>
<td>USD, 2014</td>
<td>low</td>
<td>$1657.11 ($1884.14)&lt;br&gt;$1413.99 ($1608.20)&lt;br&gt;$243.11 ($276.12)</td>
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<tr>
<td>Curtis et al [29]&lt;br&gt;2017&lt;br&gt;US</td>
<td>Retrospective analysis&lt;br&gt;Follow Up: 3 years&lt;br&gt;Sample Size: 228074</td>
<td>PDC&lt;br&gt;PDC80% = adherent</td>
<td>Total costs&lt;br&gt;Outpatient costs&lt;br&gt;Hospitalization costs</td>
<td>adjusted&lt;br&gt;all cause&lt;br&gt;disease state specific</td>
<td>USD, 2014</td>
<td>medium</td>
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For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egede et al[30] 2012 US</td>
<td>Retrospective cohort study</td>
<td>5 years</td>
<td>740195 (A:427390, NA:312805)</td>
<td>MPR</td>
<td>unadjusted</td>
<td>TC: $38633 ($39020.09), OC: $16964 ($17134), PC: $9390 ($9484.08), ACC: $12153 ($12274.77)</td>
</tr>
<tr>
<td>Gentil et al[31] 2015 Canada</td>
<td>Retrospective, observational cohort analysis</td>
<td>1 year</td>
<td>301 (A:224, NA:77)</td>
<td>MPR</td>
<td>all cause and disease state specific</td>
<td>Adjusted all cause: TC: $11124 ($9818.67), IC: $7419 ($6548.43), OC: $2687 ($2371.70), PC: $504 ($444.86), POC: $513 ($452.80), Adjusted disease state specific: TC: $4477 ($3951.65), IC: $2836 ($2503.21), OC: $1518 ($1339.87),</td>
</tr>
</tbody>
</table>

**Method of Assessment:**
- Healthcare claims data
- Pharmacy claims data

**Costs: Acute care costs**

- TC: $38633 ($39020.09)
- OC: $16964 ($17134)
- PC: $9390 ($9484.08)
- ACC: $12153 ($12274.77)

**Costs: Unadjusted costs**

- IC: $14515.24 ($17886.40)
- OC: $3599.27 ($4434.16)
- PC: $1073.12 ($1322.42)

**Quality:**
- High

**Classification:**
- Cost outcome description

---

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### Hagen et al [32]

2014  
US  
To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/short term disability costs  

<table>
<thead>
<tr>
<th>Design: Retrospective, observational cohort analysis</th>
<th>Measure: PDC Classification: PDC≥80% = compliant, PDC&lt;80% = noncompliant</th>
<th>Healthcare costs</th>
<th>Pharmacy costs</th>
<th>Medical costs</th>
<th>Short term disability costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow Up: 1 year</td>
<td></td>
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</tbody>
</table>

| Sample Size: 4978 (A:2820, NA:2158) |

<table>
<thead>
<tr>
<th>Type of Costs:</th>
<th>adjusted and unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification:</td>
<td>all cause and disease state specific</td>
</tr>
</tbody>
</table>

| Currency Year: | USD, 2003 |

<table>
<thead>
<tr>
<th>Cost of Nonadherence:</th>
<th>Adjusted all cause: PC: $1668 ($2065.99), Adjusted disease state specific: HC: $7642 ($9465.39), PC: $614 ($760.50), MC: $5974 ($7399.40), STDC: $1840 ($2279.03)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted all cause: PC: $1727 ($2139.06)</td>
<td></td>
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</tbody>
</table>

| Unadjusted disease state specific: HC: $6919 ($8569.88), PC: $785 ($972.30), MC: $5192 ($6430.82), STDC: $1717 ($2126.68) |

### Hansen et al [33]

2010  
To compare all cause total health care costs  

<table>
<thead>
<tr>
<th>Design: Retrospective, cohort study</th>
<th>Measure: MPR Classification:</th>
<th>Total Healthcare</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Type of Costs:</th>
<th>adjusted and unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification:</td>
<td>all cause and disease state specific</td>
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</tbody>
</table>

| Quality: medium |

| Classification: | cost |

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<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>MPR ≥ 80%</th>
<th>MPR &lt; 80%</th>
<th>Method of Assessment</th>
<th>Total Costs</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>2011</td>
<td>South Korea</td>
<td>Retrospective, cohort study</td>
<td>3 years</td>
<td>40082 (A:11800, NA:28282)</td>
<td>adherent</td>
<td>nonadherent</td>
<td>pharmacy claims data</td>
<td>Hospitalization costs</td>
<td>unadjusted</td>
<td>KRW, 2007</td>
<td>TC:₩765453 ($1142.31), HC:₩397549 ($593.28)</td>
</tr>
</tbody>
</table>

To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.

How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or decreased costs?

**Follow Up:** 2 years  
**Sample Size:** 108592 (A:63830, NA:44762)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 3 years  
**Sample Size:** 40082 (A:11800, NA:28282)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** unclear  
**Sample Size:** 135639 (A:99976, NA:36553)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Cost of Nonadherence:**  
**Adjusted all cause:**  
THC:$13258 ($15911.01)  
**Adjusted disease state specific:**  
THC:$2284 ($2741.04)  
**Unadjusted all cause:**  
THC:$15448.50 ($18539.90), IC:$4242.33 ($5091.25), OC:$7377.83, PC:$3828  
**Unadjusted disease state specific:**  
THC:$3232.33 ($3879.15), IC:$873.50 ($1048.29), OC:$1545.67 ($1854.96), PC:$812.67 ($975.29)  

**Design:** Retrospective, cohort study  
**Sample Size:** 40082 (A:11800, NA:28282)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Design:** Retrospective, observational claims analysis  
**Sample Size:** 135639 (A:99976, NA:36553)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Design:** Retrospective, cohort study  
**Sample Size:** 108592 (A:63830, NA:44762)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 2 years  
**Sample Size:** 108592 (A:63830, NA:44762)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 3 years  
**Sample Size:** 40082 (A:11800, NA:28282)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** unclear  
**Sample Size:** 135639 (A:99976, NA:36553)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 2 years  
**Sample Size:** 108592 (A:63830, NA:44762)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 3 years  
**Sample Size:** 40082 (A:11800, NA:28282)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** unclear  
**Sample Size:** 135639 (A:99976, NA:36553)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 2 years  
**Sample Size:** 108592 (A:63830, NA:44762)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** 3 years  
**Sample Size:** 40082 (A:11800, NA:28282)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data  

**Follow Up:** unclear  
**Sample Size:** 135639 (A:99976, NA:36553)  
**MPR ≥ 80% = adherent,**  
**MPR < 80% = nonadherent**  
**Method of Assessment:** pharmacy claims data
decreased hospitalizations or emergency department visits? Are there certain subgroups of populations that seem to benefit more than others when they adhere to their medication? What are the financial implications of changes in adherence for the nation at large and for Medicare?

White et al.[36] 2004 US

To assess the relationship between diabetic medication adherence, total healthcare costs and utilisation with patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease.

**Design:** Retrospective, database analysis

**Follow Up:** 1 year

**Sample Size:** 67029

- (>95:20170, 75-95: 14074, <75:16713)

**Measure:** MPR

**Classification:**

- MPR≥95%, MPR>75%<95%, MPR<75%

**Method of Assessment:** pharmacy claims data

**Total costs**

- **Pharmacy costs**
  - **Cost of Non-adherence:** adjusted:
    - TC(≥95): $4835 ($6518.17),
    - TC(75-95): $5314 ($7163.92),
    - TC(<75): $5706 ($7692.38),
  - **PC(≥95): $1429 ($1926.47),**
  - **PC(75-95): $1157 ($1559.78),**
  - **PC(<75): $762 ($1027.27),**
  - **NPC(≥95): $3406 ($4591.70),**
  - **NPC(75-95): $4157 ($5604.14),**
  - **NPC(<75): $4944 ($6665.11)**

  **Unadjusted:**
  - TC(≥95): $4809 ($6483.12),
  - TC(75-95): $5333 ($7189.53),
  - TC(<75): $5605 ($7556.22)

**Type of Costs:** adjusted and unadjusted

**Classification:** disease state specific

**Currency Year:** USD, 2000

**Cost of Non-adherence:** adjusted:

- TC(≥95): $4835 ($6518.17),
- TC(75-95): $5314 ($7163.92),
- TC(<75): $5706 ($7692.38),
- PC(≥95): $1429 ($1926.47),
- PC(75-95): $1157 ($1559.78),
- PC(<75): $762 ($1027.27),
- NPC(≥95): $3406 ($4591.70),
- NPC(75-95): $4157 ($5604.14),
- NPC(<75): $4944 ($6665.11)

**Quality:** low

**Classification:** cost analysis
To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.

**Design:** Retrospective, cohort study  
**Follow Up:** 1 year  
**Sample Size:** 2354 (A:830, NA:1524)

**Measure:** MPR  
**Classification:** MPR≥80% = high compliance, MPR<80% = low compliance  
**Subgroup Analysis:** commercial and Medicare supplemental  
**Method of Assessment:** pharmacy claims data

**Type of Costs:** adjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 2006

**Cost of Nonadherence:** adjusted all cause:
- THC(com): $32407 ($37732.29),  
- THC(med): $24622 ($28668.02),  
- IC(com): $2851 ($14692.74),  
- IC(med): $754 ($7863.85),  
- OC(com): $1888 ($13841.50),  
- OC(med): $10598 ($12339.52),  
- PC(com): $2667 ($8926.88),  
- PC(med): $270 ($8464.65)

**Adjusted disease state specific:**
- Diabetes:  
  - THC(com): $10024 ($11671.20),  
  - THC(med): $5015 ($5839.09),  
  - IC(com): $2323 ($2598.77),  
  - IC(med): $2606 ($3034.23),  
  - OC(com): $989 ($2315.84),  
  - OC(med): $231 ($1433.28),  
  - PC(com): $351 ($1689.44),  
  - PC(med): $379 ($1372.74)
- DPNP:  
  - THC(com): $3565 ($4150.82),  
  - THC(med): $2384 ($2775.75),
### Osteoporosis

**Briesacher et al[38]**

**2007**

**US**

To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.

<table>
<thead>
<tr>
<th>Measure: MPR</th>
<th>Total costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification: 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent</td>
<td></td>
</tr>
<tr>
<td>Inpatient costs</td>
<td></td>
</tr>
<tr>
<td>Pharmacy costs</td>
<td></td>
</tr>
</tbody>
</table>

**Type of costs: adjusted and unadjusted**

**Classification: disease state specific**

**Currency Year: USD, 2004**

**Cost of Nonadherence**: adjusted:

<table>
<thead>
<tr>
<th>IC(com):$1739 ($2024.76), IC(med):$1048 ($1220.21), OC(com):$362 ($421.49), OC(med):$181 ($210.74), PC(com):$1464 ($1704.57), PC(med):$1155 ($1344.80)</th>
</tr>
</thead>
</table>

**Unadjusted**

<table>
<thead>
<tr>
<th>IC(com):$1739 ($2024.76), IC(med):$1048 ($1220.21), OC(com):$362 ($421.49), OC(med):$181 ($210.74), PC(com):$1464 ($1704.57), PC(med):$1155 ($1344.80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC(80-100):$1273 (-$1576.74), TC(60-79):$294 (-$364.15), TC(40-59):$573 (-$709.72), TC(20-39):$101 ($125.10), IC(80-100):$883 (-$1093.68),</td>
</tr>
</tbody>
</table>

**Quality: medium**

**Classification: cost description**
Eisenberg et al[39] 2015 US
To determine healthcare outcomes associated with compliance and noncompliance to bisphosphonate therapy in women diagnosed with osteoporosis

Design: Retrospective claims study
Follow Up: 2 years
Sample Size: 27905 (A:11368, NA:16537)

Measure: MPR
Classification: (≥70% = compliant, <70% = noncompliant)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Physician office visit costs

Type of Costs: unadjusted
Classification: all cause and disease state specific
Currency Year: USD, 2012
Cost of Nonadherence: all cause:
TC:$7237 ($7550.72), IC:$1986 ($2072.09), OC:$2057 ($2146.17), EDC:$258 ($269.18), PC:$2197 ($2292.24), POC:$738 ($769.99)
Disease state specific:
TC:$674 ($703.22), IC:$334 ($348.48), OC:$77 ($80.34), EDC:$5 ($5.22), PC:$213 ($222.23), POC:$44 ($45.91)

Halpern et al[40] 2011 US
To examine the associations of adherence to osteoporosis therapies

Design: Retrospective analysis
Follow Up: 540 days
Sample Size: 21655

Measure: MPR
Classification: (≥80% = high adherence,)

Medical costs

Type of Costs: unadjusted
Classification: all cause
Currency Year: USD, 2006
Cost of Nonadherence: commercial:
Hazel-Fernandez et al [41]

To evaluate the healthcare utilisation patterns of Medicare part D beneficiaries newly initiating teriparatide and to assess the association of medication adherence and persistence with bone fracture.

**Design:** Retrospective cohort study

**Follow Up:** 12 months

**Sample Size:** 761

(≥80%: 163, ≥50<80%: 57, <50%: 541)

**Classification:**

- ≥80% = high adherence
- ≥50<80% = moderate adherence
- <50% = low adherence

**Method of Assessment:** pharmacy claims data

---

**Type of Costs:** unadjusted

**Classification:** disease state specific and fracture related

**Currency Year:** USD, 2010

**Cost of Nonadherence**:

- **Disease state specific**:
  - THC(≥80): $21033 ($22942.39),
  - THC(50-80): $25574 ($27895.62),
  - THC(<50): $15528 ($16937.64),
  - IC(≥80): $2198 ($2397.54),
  - IC(50-80): $3448 ($3924.91),
  - IC(<50): $4897 ($5341.55),
  - OC(≥80): $5151 ($5618.61),
  - OC(50-80): $6439 ($7023.54),
  - OC(<50): $806 ($8333.07),
  - EDC(≥80): $2011 ($230.15),
  - EDC(50-80): $330 ($359.96),
  - EDC(<50): $8465 ($507.21),
  - PC(≥80): $3472 ($4756.89),
  - PC(50-80): $10358 ($11298.31),
  - PC(<50): $4361 ($4756.89)

- **Fracture related**:
  - THC(≥80): $12670 ($13820.19),
  - THC(50-80): $9292 ($10135.53),
  - THC(<50): $4419 ($4820.16)

---

≥50<80% = moderate adherence, <50% = low adherence

≥80%: 8759, ≥50<80%: 5237, <50%: 7659

≥80%: $5000.78, ≥50<80%: $5468.84, <50%: $6515.56

MC(≥80): $4295 ($5000.78),
MC(50-80): $4697 ($5468.84),
MC(<50): $5596 ($6515.56)

Medicare:
MC(≥80): $590 ($5344.25),
MC(50-80): $5536 ($6445.71),
MC(<50): $5801 ($6754.25)

Measure:
PDC

Classification:
(≥80% = high adherence,
≥50<80% = moderate adherence,
<50% = low adherence

Method of Assessment:
pharmacy claims data

Quality: medium

Classification: cost outcome description
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huybrechts et al[42]</td>
<td>2006</td>
<td>US</td>
<td>To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.</td>
<td>Retrospective cohort study</td>
<td>5 years</td>
<td>38120</td>
<td>MPR</td>
<td>≥80% = compliant, &lt;50% = noncompliant</td>
<td>unadjusted</td>
<td>TC:$7200 ($9706.44), MC:$1476 ($1989.84), InstC:$5736 ($7732.80)</td>
</tr>
<tr>
<td>Kjellberge et al[43]</td>
<td>2016</td>
<td>Denmark</td>
<td>To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of noncompliance with health care resource use and cost.</td>
<td>Retrospective cohort study</td>
<td>1 year</td>
<td>38234</td>
<td>MPR</td>
<td>≥70% = compliant, &lt;70% = noncompliant</td>
<td>adjusted</td>
<td>all cause: TC:€4933 ($6209.58), MC:€3471 ($4369.20), Disease state specific: TC:€754 ($949.12), MC:€426 ($536.24)</td>
</tr>
<tr>
<td>Modi et al[44]</td>
<td>2015</td>
<td></td>
<td>To evaluate compliance with</td>
<td>Retrospective cohort study</td>
<td></td>
<td></td>
<td>MPR</td>
<td>Classification</td>
<td>unadjusted</td>
<td></td>
</tr>
</tbody>
</table>

Quality: low Classification: cost description

Quality: high Classification: cost outcome description

Quality: medium Classification: cost description
US osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance

Follow Up: 1 year
Sample Size: 27913 (A:23430, NA:34483)

(≥80% = compliant, <80% = noncompliant)

Method of Assessment: healthcare claims data

Outpatient costs ED costs Pharmacy costs Medical costs Other costs

state specific

Cost of Nonadherence: all cause:
TC:$11749 ($12,484.12),
IC:$8768 ($9,316.60),
OC:$3945 ($4,191.83),
EDC:$104 ($110.51),
PC:$2981 ($3,167.52),
MC:$8768 ($9,316.60),
Otc:$997 ($1,059.38)

Disease state specific:
TC:$630 ($669.42),
IC:$443 ($4,70.72),
OC:$158 ($1,67.89),
EDC:$3 ($3.19),
PC:$325 ($3,45.33),
Otc:$26 ($27.63)

Olsen et al[45]
2013 Denmark

To assess the association between refill compliance and all cause health care costs.

Design: Retrospective observational study
Follow Up: 2 years
Sample Size: 47176 (not specified)

Measure: MPR
Classification:
(≥80% = optimal compliance,
>50<80% = suboptimal compliance, <50% = low compliance

Method of Assessment: pharmacy claims data

Fracture costs

Type of Costs: unadjusted
Classification: fracture site specific
Currency Year: DKK, 2010

Cost of Nonadherence:
Hip fracture:
FC(50-80):kr17,575.50 ($2,453.14),
FC(<50):kr5,495.45 ($749,987.04)
Spine fracture:
FC(50-80):kr17,470.00 ($2,156.82),
FC(<50):kr2,647.22 ($279,59.14)
Humerus fracture:
FC(50-80):kr11,776.50 ($1,454.12),
FC(<50):kr9,521.75 ($981,73.70)
Forearm fracture:
FC(50-80):kr4,630.24 ($571,62.70),
FC(<50):kr5,072.50 ($866.81)

Quality: medium
Sunycz et al [46] 2008 US

To examine the relationship between persistence and compliance with bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naïve users.

**Design:** Retrospective observational study  
**Follow Up:** 3 years  
**Sample Size:** 32944 (A:12186, NA:20758)

**Measure:** MPR  
**Classification:**  
(≥80% = compliant, <80% = noncompliant)

**Method of Assessment:** pharmacy claims data

**Total healthcare costs**  
Inpatient costs  
Outpatient costs  
ED costs  
Pharmacy costs  
Radiology costs

**Type of Costs:** unadjusted  
**Currency Year:** USD, 2005  
**Cost of Nonadherence:**
- All cause:  
  THC:$23660 ($28394.52),  
  IC:$18839 ($22608.81),  
  OC:$10061 ($12074.27),  
  EDC:$832 ($988.49),  
  PC:$6941 ($8329.94),  
  RC:$1079 ($1294.91)
- Disease state specific:  
  THC:$1602 ($1922.57),  
  IC:$14074 ($16890.30),  
  OC:$501 ($601.25),  
  EDC:$452 ($542.45),  
  PC:$918 ($1101.70),  
  RC:$184 ($220.82)

**Quality:** low  
**Classification:** cost description

Zhao et al [47] 2014 US

To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.

**Design:** Retrospective cohort study  
**Follow Up:** 36 months  
**Sample Size:** 824 (≥80:362, 50-80%:219, <50%:243)

**Measure:** PDC  
**Classification:**  
(≥80% = high, 50-80% = medium, <50% = low)

**Method of Assessment:** pharmacy claims data

**Total healthcare costs**  
Inpatient costs  
Outpatient costs  
ED costs  
Pharmacy costs

**Type of Costs:** adjusted and unadjusted  
**Currency Year:** USD, 2010  
**Cost of Nonadherence:**
- Adjusted:  
  THC(≥80):$34428 ($37553.4),  
  THC(50-80):$37956 ($41401.68),  
  THC(<50):$11188 ($34019.28),  
  IC(≥80):$5788 ($8233.20),  
  IC(50-80):$11520 ($1256.80),  
  IC(<50):$10556 ($12605.04)
- Disease state specific:  
  THC(≥80):$19479 ($22457.51),  
  THC(50-80):$20830 ($23935.34),  
  THC(<50):$10556 ($12605.04)

**Quality:** medium  
**Classification:** cost description
To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients.

**Design:** Retrospective observational cohort study  
**Follow Up:** 36 months  
**Sample Size:** 1568  
(≥80: 783, 50-80%: 382, <50%: 403)

**Measure:** PDC  
**Classification:** (≥80% = high, 50-80% = medium, <50% = low)

**Method of Assessment:** pharmacy claims data

**Total healthcare costs**  
<table>
<thead>
<tr>
<th>Classification</th>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
<th>Pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC(≥80)</td>
<td>$87464 ($40865.04),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC(50-80%)</td>
<td>$35076 ($38260.20),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC(&lt;50%)</td>
<td>$29484 ($32160.60),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC(≥80)</td>
<td>$7392 ($7735.80),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC(50-80%)</td>
<td>$11100 ($12107.64),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC(&lt;50%)</td>
<td>$10500 ($11597.16),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC(≥80)</td>
<td>$12924 ($14097.24),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC(50-80%)</td>
<td>$14928 ($16283.16),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC(&lt;50%)</td>
<td>$17568 ($19162.80),</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type of Costs:** adjusted and unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2010  
**Cost of Nonadherence:**

**Adjusted:**
| Classification | | |
| THC(≥80) | $40212 ($43862.52), | |
| THC(50-80%) | $40512 ($44189.76), | |
| THC(<50%) | $40128 ($43770.84), | |
| IC(≥80) | $8136 ($8874.60), | |
| IC(50-80%) | $12060 ($13154.76), | |
| IC(<50%) | $15444 ($18304.36), | |
| OC(≥80) | $12924 ($14097.24), | |
| OC(50-80%) | $14928 ($16283.16), | |
| OC(<50%) | $17568 ($19162.80), | |

**Quality:** medium  
**Classification:** cost description
To assess the association between adherence levels to different inhaled corticosteroid/long acting β₂-adrenergic agonist and COPD exacerbation rates and costs in commercially insured population

**Design:** Observational cohort study  
**Follow Up:** 12 months  
**Sample Size:** 13657  
(≥80%: 1898, ≥50<80%: 1971, ≥30 <50%: 2443, <30% :7345)

**Measure:** PDC Classification: (≥80 = adherent, ≥50<80% = mildly nonadherent, ≥30 <50% = moderately nonadherent, <30% highly nonadherent)  
**Method of Assessment:** commercially insured healthcare claims data  
**Total costs:**  
- **Outpatient costs**  
  - PC(≥80): $29392 ($21152.40),  
  - PC(50-80): $13908 ($15170.52),  
  - PC(<50): $8700 ($9843.24)  
- **Pharmacy costs**  
  - THC(≥80): $27678 ($46650.48),  
  - THC(50-80): $36780 ($40118.88),  
  - THC(<50): $39792 ($43404.36)  
- **Hospitalization costs**  
  - IC(≥80): $7620 ($8311.80),  
  - IC(50-80): $12228 ($13338.12),  
  - IC(<50): $15768 ($17199.48)  
- **OC(≥80): $14580 ($15903.60),  
  - OC(50-80): $12108 ($13207.20),  
  - OC(<50): $15324 ($16715.16)  

**Type of Costs:** adjusted  
**Classification:** all cause and disease state specific  
**Currency Year:** USD, 2014  
**Cost of Nonadherence:**  
- All cause:  
  - TC(≥80): $25446 ($22772.24),  
  - TC(50-80): $25545 ($25800.95),  
  - TC(30-50): $34303 ($24546.51),  
  - TC(<30): $25148 ($25399.98)  
- OC(≥80): $8616 ($7894.31),  
- OC(50-80): $8225 ($8307.41),  
- OC(30-50): $8365 ($8448.81),  
- OC(<30): $8857 ($8945.74)  
- PC(≥80): $7854 ($8033.70),  

**Quality:** medium  
**Classification:** cost description
### Delea et al[50]

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Sample Size Classification</th>
<th>Measure</th>
<th>Classification</th>
<th>Total costs</th>
<th>Type of Costs</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>US</td>
<td>Retrospective longitudinal cohort study</td>
<td>24 months</td>
<td>12907 (≥75: 2612, 50-75%: 3608, 25-50%: 5035, &lt;25%: 1652)</td>
<td>MPR Classification: (≥75, 50-75%, 25-50%, &lt;25%)</td>
<td>Pharmacy claims data</td>
<td>Disease state specific:</td>
<td></td>
<td>unadjusted</td>
<td>medium</td>
</tr>
</tbody>
</table>

**Type of Costs:** unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2003  
**Cost of Nonadherence:**  
- TC(≥75): $8075.33 ($8156.24)  
- TC(50-75): $7053 ($7123.67)  
- TC(30-50): $6623 ($6689.36)  
- TC(<30): $5644 ($5700.55)  
- OC(≥75): $2194.33 ($2216.32)  
- OC(50-75): $1947 ($1966.51)  
- OC(30-50): $1997 ($2017.01)  
- OC(<30): $2152 ($2173.56)  

**Total costs: Total outpatient costs + ED costs + Other costs**
patients in typical US clinical practice.

**Diehl et al[51]**
2010
US

To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and received palivizumab in accordance with the dosing schedule recommended by the American Academy of Paediatrics in 2006 versus those who did not.

**Design:** Retrospective claims analysis
**Follow Up:** 7 months
**Sample Size:** 245 (A:73, NA:172)

**Measure:** 37 day gap in claims
**Classification:** (>37 day gap in claims = noncompliant)

**Method of Assessment:** pharmacy claims data

**Total costs**
- **Pharmacy costs**
  - OC(50-75): $852 ($1084.21),
  - OC(25-50): $600 ($763.53),
  - OC(<25): $388 ($493.75),
  - EDC(≥75): $32 ($40.72),
  - EDC(50-75): $36 ($45.81),
  - EDC(25-50): $60 ($76.35),
  - EDC(<25): $48 ($61.08),
  - OtC(≥75): $292 ($371.59),
  - OtC(50-75): $276 ($351.22),
  - OtC(25-50): $300 ($381.77),
  - OtC(<25): $240 ($305.41)

**Cost of Nonadherence:**
- **TC:** $19093.46 ($21656.12),
- **PC:** $7647.40 ($8673.81),
- **SC:** $11604.03 ($13161.45)

**Quality:** medium
**Classification:** cost description

**Joshi et al[52]**
2006
US

Examine the association of medication adherence with workplace productivity and health related quality of life in asthma patients.

**Design:** quantitative analysis
**Follow Up:** 7 months
**Sample Size:** 385 (high:150, medium:73, low: 162)

**Measure:** Morisky scale
**Classification:** (0= high adherence, 1-2 = medium adherence, >2 = low adherence)

**Method of Assessment:**

**Total productivity cost**
- **Absenteeism costs**
  - TPC(0): $1256.90 ($1571.73),
  - TPC(1-2): $1282.50 ($1854.17),
  - TPC(>2): $1873.10 ($1392.87),
- **Presenteeism costs**
  - AbC(0): $638.70 ($822.53),
  - AbC(1-2): $608.90 ($790.34)

**Type of Costs:** unadjusted
**Classification:** disease state specific
**Currency Year:** USD, 2002

**Cost of Nonadherence**
- **TPC:** $1256.90 ($1571.73),
- **PC:** $1282.50 ($1854.17),
- **Sc:** $1873.10 ($1392.87),
- **AbC:** $638.70 ($822.53),
- **AbC:** $608.90 ($790.34)

**Quality:** medium
**Classification:** cost outcome description
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Measure</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miravitlles et al [53] 2013 Spain</td>
<td>multicentre, retrospective, observational study</td>
<td>GOLD 2007 Guidelines</td>
<td>(adherent, nonadherent)</td>
<td>GOLD guidelines</td>
<td>unadjusted</td>
<td>EUR, 2009</td>
<td>EDC:€40.83 ($57.91), PC:€771.50 ($1094.27), POC:€106.29 ($150.76), HC:€101.61 ($144.12)</td>
<td>medium</td>
</tr>
<tr>
<td>Quittner et al [54] 2014 US</td>
<td>retrospective, cohort study</td>
<td>MPR</td>
<td>(≥80% = high adherence, 50-80% = moderate adherence, &lt;50% = low adherence)</td>
<td>pharmacy claims data</td>
<td>unadjusted</td>
<td>USD, 2011</td>
<td>THC(≥80%): $5749.50 ($38244.05), THC(50-80%): $45031.50 ($48173.73), THC(&lt;50%): $30284.50 ($53793.28)</td>
<td>medium</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
### Assessment:

**HC:** $6893 ($8537.68)

**Disease state specific:**
- **OC:** $3931 ($4868.94)
- **EDC:** $91 ($112.71)
- **PC:** $18751 ($23225.01)
- **MC:** $10243 ($12686.99)
- **HC:** $4494 ($5566.27)

**Quality:** high

**Classification:** cost description

---

**Mitra et al** [58]

2012 US

To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.

**Design:** retrospective, observational cohort study

**Follow Up:** 12 months

**Sample Size:** 1693 (A:476, NA:1216)

**Measure:** MPR

**Classification:**
- (≥80% = adherent, <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2010

**Cost of Nonadherence:**
- All cause: TC:$28726.65 ($31334.47)
- Disease state specific:
  - **IC:** $17634.67 ($19467.76)
  - **OC:** $10909 ($12043.43)
  - **EDC:** $458 ($505.63)
  - **PC:** $18410 ($20324.46)

**Wan et al** [59]

2014 US

To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.

**Design:** retrospective cohort analysis

**Follow Up:** 360 days

**Sample Size:** 1646 (A:674, NA:972)

**Measure:** MPR

**Classification:**
- (≥80% = adherent, <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Type of Costs:** adjusted

**Classification:** all cause and disease state specific

**Currency Year:** USD, 2009

**Cost of Nonadherence:**
- All cause: TC:$47411 ($52341.27)
- Disease state specific:
  - **TC:** $23252.36 ($25903.96)
  - **IC:** $17634.67 ($19467.76)
  - **OC:** $10909 ($12043.43)
  - **EDC:** $458 ($505.63)
  - **PC:** $18410 ($20324.46)
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Method of Assessment</th>
<th>Total Costs</th>
<th>Type of Costs</th>
<th>Currency Year</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>Davis et al[60]</td>
<td>2008</td>
<td>US</td>
<td></td>
<td>Retrospective claims analysis</td>
<td>12 months</td>
<td>10892 (A:6644, NA:4248)</td>
<td>MPR</td>
<td>≥80% = adherent, &lt;80% = nonadherent</td>
<td>Pharmacy claims data</td>
<td>TC:$33652 ($37151.47), THC:$18764 ($20715.27), IC:$12564 ($13870.53), OC:$5890 ($6502.50), EDC:$48 ($52.99), PC:$15150 ($16725.45)</td>
<td>Unadjusted</td>
<td>Disease state specific</td>
<td>USD, 2003</td>
<td></td>
<td>Medium</td>
<td>Cost</td>
</tr>
<tr>
<td>Ettinger et al[61]</td>
<td>2009</td>
<td>US</td>
<td></td>
<td>Retrospective claims analysis</td>
<td>12 months</td>
<td>1278 (A:758, NA:520)</td>
<td>MPR</td>
<td>≥80% = adherent, &lt;80% = nonadherent</td>
<td>Pharmacy claims data</td>
<td>TC:$17817 ($22673.06), IC:$2714 ($3453.71), EDC:$526 ($669.36), PC:$347 ($441.58), PO: $3063 ($3897.83), AC:$8344 ($10618.18), OtPC:$2828 ($3591.14)</td>
<td>Unadjusted</td>
<td>Disease state specific</td>
<td>USD, 2003</td>
<td></td>
<td>Medium</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>Faught et al[62]</td>
<td>2009</td>
<td>US</td>
<td></td>
<td>Retrospective observational open cohort design</td>
<td></td>
<td></td>
<td>MPR</td>
<td>≥80% = adherent</td>
<td>Pharmacy claims data</td>
<td>TC:$1466 ($1865.56), IC:$1799 ($2289.32), EDC:$260 ($330.86), PC-$71 ($90.35), OtPC-$358 ($455.57)</td>
<td>Unadjusted</td>
<td>Disease state specific</td>
<td>USD, 2003</td>
<td></td>
<td>Medium</td>
<td>Cost</td>
<td></td>
</tr>
</tbody>
</table>

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For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
**For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml**

**Pruitt et al[65]**

2015 US

To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.

**Design:** retrospective cohort study  
**Follow Up:** 2 years  
**Sample Size:** 502 (A:56, NA:176)

**Measure:** MPR  
**Classification:**  
(≥90% = adherent, <90% = nonadherent)  
**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2009  
**Cost of Nonadherence:**  
HIV:  
TC:$15360 ($16957.32),  
IC:$3864 ($4265.76),  
OC:$3948 ($4358.52),  
PC:$4956 ($5471.40),  
OtPC:$1764 ($1947.48),  
BHIC:$840 ($927.36)

AIDS:  
TC:$27648 ($30523.08),  
IC:$13008 ($14360.76),  
OC:$5880 ($6491.52),  
PC:$5640 ($6226.56),  
OtPC:$2580 ($2848.32),  
BHIC:$528 ($582.96)

**Quality:** medium  
**Classification:** cost description

---

**Parkinson’s Disease**

**Davis et al[66]**

2010 US

To assess the extent to which patients diagnosed with Parkinson’s disease are non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.

**Design:** retrospective administrative claims study  
**Follow Up:** 12 months  
**Sample Size:** 3119 (A:1211, NA:1908)

**Measure:** MPR  
**Classification:**  
(≥80% = adherent, <80% = nonadherent)  
**Method of Assessment:** pharmacy claims data

**Type of Costs:** unadjusted  
**Classification:** disease state specific  
**Currency Year:** USD, 2001  
**Cost of Nonadherence:**  
TC:$18511 ($24262.36),  
PC:$2684 ($3537.36),  
MC:$15827 ($20859.12)

**Quality:** medium  
**Classification:** cost outcome description

---

**Delea et al[67]**

2011 US

To assess the associations between adherence to

**Design:** retrospective historical cohort study  
**Follow Up:** 12 months  
**Sample Size:**

**Measure:** PDC  
**Classification:**  
(≥80% = adherent)  
**Type of Costs:** adjusted and unadjusted  
**Classification:** all cause and disease state specific

**Quality:** high  
**Classification:** cost description
### Sample Size:

| A:617 | NA:598 |

Sample Size: 1215 (A:617, NA:598)

### Method of Assessment:

- Pharmacy claims data

### Costs

#### Other costs

- **Currency Year:** USD, 2005
- **Cost of Nonadherence:**
  - Adjusted all cause:
    - TC: $19686 ($23625.30),
    - IC: $5954 ($7145.43),
    - PC: $6391 ($7669.88),
    - OtC: $8795 ($10554.94)
  - Adjusted disease state specific:
    - TC: $8574 ($10289.71),
    - IC: $3705 ($4446.39),
    - PC: $3850 ($4620.41),
    - OtC: $1884 ($2261)
- Unadjusted all cause:
  - TC: $19362 ($23236.46),
  - IC: $5463 ($6556.18),
  - PC: $6158 ($7390.26),
  - OtC: $7740 ($9288.82)
- Unadjusted disease state specific:
  - TC: $9156 ($10988.18),
  - IC: $3238 ($3885.94),
  - PC: $3789 ($4547.20),
  - OtC: $2129 ($2555.03)

#### Type of Costs:

- **Class:** unadjusted
- **Classification:** disease state specific
- **Currency Year:** USD, 2007
- **Cost of Nonadherence:**
  - TC(90-100): $36407 ($41293.43),
  - TC(80-89): $43417 ($49244.29),
  - TC(≤79): $45867 ($52023.13),
  - IC(90-100): $15294 ($17346.71),
  - IC(80-89): $21603 ($24502.49),
  - IC(≤79): $24727 ($28045.78),
  - OC(90-100): $10155 ($11517.97),
  - OC(80-89): $17155 ($20086.49),
  - OC(≤79): $20165 ($23425.88)

### Design:

- **Type:** retrospective cross-sectional study
- **Follow Up:** 19 months

### Measure:

- **MPR Classification:**
  - (>90<100% = high, 80-89% = moderate, ≤79% = low)
- **Method of Assessment:**
  - Pharmacy claims data

### Quality:

- **Classification:** cost description

---

Wei et al.[68]

To examine the associations of adherence to antiparkinson drugs with healthcare utilisation and economic outcomes.
Musculoskeletal

Ivanova et al[69]

2012
US

To compare the rates of severe relapse and total direct and indirect costs over a 2 year period between US based employees with MS who were adherent and non-adherent to disease modifying drugs.

Design: retrospective cohort study
Follow Up: 2 years
Sample Size: 648 (A:448, NA:200)

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Method of Assessment: pharmacy claims data

Total costs
Total healthcare costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Medical costs
Short term disability costs
Absenteeism cost

Type of Costs: unadjusted
Classification: all cause, disease state specific and indirect
Currency Year: USD, 2007
Cost of Nonadherence:
All cause:
TC:$8079 ($9276.76),
THC:$6022 ($6830.25),
IC:$1030.50 ($1168.81),
OC:$3231 ($3664.65),
EDC:$143.50 ($162.76),
PC:$1617 ($1834.03),
MC:$4405.50 ($4996.79)
Disease state specific:
TC:$3005 ($3408.32),
IC:$505 ($572.78),
OC:$1710 ($1939.51),
EDC:$37 ($41.97),
PC:$753 ($854.07),
MC:$2252 ($2554.26)
Indirect:
STDC:$1234 ($1396.22),
AbC:$826 ($936.86)

Quality: high
Classification: cost outcome description

Tan et al[70]

2011
US

To assess the impact of treatment adherence on MS related hospitalizations

Design: retrospective cohort study
Follow Up: 12 months
Sample Size: 2446

Measure: MPR
Classification: (≥80% = adherent, <80% = nonadherent)

Medical costs

Type of Costs: adjusted and unadjusted
Classification: disease state specific
Currency Year: USD, 2007
Cost of Nonadherence:

Quality: medium
Classification: cost outcome description
To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.

**Design:** retrospective cohort analysis

**Follow Up:** 12 months

**Sample Size:** 5435

(A:1744, NA:3691)

**Measure:** MPR

**Classification:**
- (≥80% = adherent,
  <80% = nonadherent)

**Method of Assessment:** pharmacy claims data

**Total costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
<th>Pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted:</strong></td>
<td>MC:$4348 ($5062.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted:</strong></td>
<td>MC:$5179 ($6030.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quality: medium

Classification: cost description

Zhao et al[71]
2011
US

Estimate the association between treatment interruptions and non-adherence with imatinib and healthcare costs for US managed care patients.

**Design:** retrospective observational cohort analysis

**Follow Up:** 12 months

**Sample Size:** 267

(95%:120, 90-95%:50-90%,<90%:69,<90%:53)

**Measure:** MPR

**Classification:**
- (≥95% = very high,
  >90%<95% = high,
  >50%<90% = intermediate,
  <50% = low)

**Method of Assessment:** pharmacy claims data

**Total costs**

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Inpatient costs</th>
<th>Outpatient costs</th>
<th>Pharmacy costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THC(≥95):</strong></td>
<td>$42250 ($52330.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>THC(90-95):</strong></td>
<td>$39236 ($48597.76)</td>
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</tr>
<tr>
<td><strong>THC(50-90):</strong></td>
<td>$54770 ($67838.19)</td>
<td></td>
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</tr>
<tr>
<td><strong>THC(&lt;50):</strong></td>
<td>$131357 ($162698.93)</td>
<td></td>
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</tr>
<tr>
<td><strong>IC(≥95):</strong></td>
<td>$1156 ($1431.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IC(90-95):</strong></td>
<td>$1362 ($1686.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IC(50-90):</strong></td>
<td>$19096 ($23652.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IC(&lt;50):</strong></td>
<td>$81572 ($101035.18)</td>
<td></td>
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</tr>
<tr>
<td><strong>OC(≥95):</strong></td>
<td>$9299 ($11517.75)</td>
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</tr>
<tr>
<td><strong>OC(90-95):</strong></td>
<td>$11148 ($13807.93)</td>
<td></td>
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</tr>
</tbody>
</table>

Quality: high

Classification: cost description

Cancer
Darkow et al[72]
2007
US
Wu et al[73] 2010 US

To examine the association between adherence with imatinib and direct healthcare costs and resource utilisation

Design: retrospective observational cohort analysis
Follow Up: 12 months
Sample Size: 592 (A:350, NA:242)

Measure: MPR
Classification: (≥85% = high adherence, <85% = low adherence)
Method of Assessment: pharmacy claims data

Total costs
Inpatient costs
Outpatient costs
ED costs
Pharmacy costs
Other pharmacy costs

Type of Costs: unadjusted
Classification: disease state specific
Currency Year: USD, 2008
Cost of Nonadherence:
TC:$107341 ($119415.73),
OC($50-90):$14631 ($18121.97),
OC($<50):$3956 ($42057.94),
EDC($≥95):$86 ($44.59),
EDC($90-95):$568 ($703.53),
EDC($50-90):$104 ($128.81),
EDC($<50):$83 ($226.66),
PC($≥95):$29056 ($35988.80),
PC($90-95):$23693 ($29346.18),
PC($50-90):$18330 ($22703.56),
PC($<50):$183 ($226.66),
MC($≥95):$10731 ($13291.43),
MC($90-95):$13452 ($16661.66),
MC($50-90):$34202 ($42362.64),
MC($<50):$116892 ($144782.57),
OtPC($≥95):$2462 ($3049.44),
OtPC($90-95):$2091 ($2589.92),
OtPC($50-90):$2238 ($2771.99),
OtPC($<50):$2238 ($2771.99),
OtC($≥95):$241 ($298.50),
OtC($90-95):$374 ($463.24),
OtC($50-90):$371 ($459.52),
OtC($<50):$1181 ($1462.79)

Quality: medium
Classification: cost description
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Objective</th>
<th>Study Design</th>
<th>Follow Up</th>
<th>Sample Size</th>
<th>Measure</th>
<th>Classification</th>
<th>Type of Costs</th>
<th>Cost of Nonadherence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>Leider et al[74]</td>
<td>2011</td>
<td>US</td>
<td>To assess the economic burden of chronic opioid users and to determine whether opioid regimen non-adherence contributes to increased healthcare costs.</td>
<td>retrospective claims based analysis</td>
<td>12 months</td>
<td>(A:442, NA:1658)</td>
<td>urine testing</td>
<td>(positive test = nonadherent, negative test = adherent)</td>
<td>unadjusted</td>
<td>THC: $26433 ($29406.43), IC: $6361 ($7076.55), OC: $9734 ($10828.97), EDC: $421 ($468.36), PC: $7960 ($8855.42), MC: $1957 ($2177.14)</td>
</tr>
<tr>
<td>Ruetsch et al[75]</td>
<td>2017</td>
<td>US</td>
<td>To examine patient characteristics and outcomes associated with nonadherence to buprenorphine and to identify specific patterns of nonadherent behaviour.</td>
<td>cross sectional, retrospective analysis</td>
<td>12 months</td>
<td>(A:172, NA:305)</td>
<td>MPR</td>
<td>(≥80% = adherent, &lt;80% = nonadherent)</td>
<td>unadjusted</td>
<td>THC: $16555 ($16995.62), IC: $5657 ($5807.57), OC: $5594 ($5742.89), EDC: $1147 ($1177.53), PC: $2365 ($2427.95), MC: $14190 ($14567.68)</td>
<td>medium</td>
</tr>
<tr>
<td>Tkacz et al[76]</td>
<td>2014</td>
<td>US</td>
<td>To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent</td>
<td>retrospective cohort analysis</td>
<td>12 months</td>
<td>(A:146, NA:309)</td>
<td>MPR</td>
<td>(≥80% = adherent, &lt;80% = nonadherent)</td>
<td>adjusted and unadjusted</td>
<td>THC: $49051 ($53503.88), IC: $26470 ($28872.96), OC: $14570 ($15892.67), EDC: $4439 ($4841.98)</td>
<td>medium</td>
</tr>
<tr>
<td>Study</td>
<td>Metabolic conditions other than diabetes mellitus</td>
<td>Blood</td>
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<tr>
<td>Lee et al [77]</td>
<td>To assess the relationship between medication adherence and healthcare costs among US patients on dialysis given cinacalcet to manage secondary hypoparathyroidism.</td>
<td>Candrilli et al [78]</td>
<td>To investigate the relationships among hydroxyurea adherence, healthcare utilisation and healthcare costs.</td>
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<tr>
<td>Design: retrospective cohort study</td>
<td>Follow Up: 12 months</td>
<td>Design: retrospective longitudinal study</td>
<td>Follow Up: 12 months</td>
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<tr>
<td>Measure: MPR</td>
<td>Total costs</td>
<td>Type of Costs: unadjusted</td>
<td>Quality: medium</td>
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<td></td>
</tr>
<tr>
<td>Classification: (≥80% = high adherent, &lt;80% = low adherent)</td>
<td>Total inpatient costs</td>
<td>Classification: all cause and disease state specific</td>
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<tr>
<td>Method of Assessment: pharmacy claims data</td>
<td>Total outpatient costs</td>
<td>Currency Year: USD, 2010</td>
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<tr>
<td></td>
<td>ED costs</td>
<td>Cost of Nonadherence: All cause:</td>
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<td></td>
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<tr>
<td></td>
<td>Pharmacy costs</td>
<td>PC:$3581 ($3906.09)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Other pharmacy costs</td>
<td>TC:$47868 ($52213.49),</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>IC:$26043 ($28407.20),</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OC:$14173 ($15459.63),</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDC:$4058 ($4426.39),</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PC:$3557 ($3879.91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
<table>
<thead>
<tr>
<th>Pharmacy Claims Data</th>
<th>Costs</th>
<th>Ancillary Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC: $9780 ($10880.15), EDC: $837 ($931.15), PC: $2579 ($2869.11), POC: $3483 ($3874.80), AC: $3911 ($4350.95)</td>
<td>Disease state specific: TC: $12097 ($13457.78), IC: $7315 ($8137.86), EDC: $552 ($614.09), PC: $158 ($175.77), POC: $1865 ($2074.79), AC: $2466 ($2743.40)</td>
<td></td>
</tr>
</tbody>
</table>

**All Alvarez Payero et al [79]**

Spain 2014

To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.

**Design:** retrospective observational study

**Follow Up:** 1527 days

**Sample Size:** 87 (A:21, NA:66)

**Measure:** pharmacy records

**Classification:** (>75% = adherent, ≤75% = nonadherent)

**Method of Assessment:** pharmacy and hospital claims data

**Hospitalization costs**

**Type of Costs:** unadjusted

**Classification:** all cause

**Currency Year:** EUR, 2012

**Cost of Nonadherence**: All cause: HC: €6275.80 ($8893.94)
costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro, DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won

*: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group; 
#: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against adherent group; ####: cost per episode of nonadherence


26. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003;11(12):817-22 doi: 10.2165/00115677-200311120-00006[published Online First: Epub Date].


34. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;49:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]].


### eTable 3: Total cost or total healthcare cost comparison across disease groups

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Min adj cost per annum per person</th>
<th>Max adj cost per annum per person</th>
<th>Median adj cost per annum per person</th>
<th>Mean adj cost per annum per person</th>
<th>No. adj studies</th>
<th>Min unadj cost per annum per person</th>
<th>Max unadj cost per annum per person</th>
<th>Median unadj cost per annum per person</th>
<th>Mean unadj cost per annum per person</th>
<th>No. unadj studies</th>
<th>Total studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>3347</td>
<td>19472</td>
<td>8080</td>
<td>9204</td>
<td>6</td>
<td>1433</td>
<td>8377.05</td>
<td>5931</td>
<td>4701</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Mental Health</td>
<td>3253</td>
<td>19363</td>
<td>11262</td>
<td>11052</td>
<td>6</td>
<td>2512</td>
<td>25920</td>
<td>17231</td>
<td>16486</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2741</td>
<td>9819</td>
<td>6907</td>
<td>6310</td>
<td>7</td>
<td>1142</td>
<td>7950</td>
<td>5594</td>
<td>4934</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>949</td>
<td>44190</td>
<td>41402</td>
<td>32866</td>
<td>4</td>
<td>669</td>
<td>43404</td>
<td>9921</td>
<td>18190</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>5701</td>
<td>7124</td>
<td>6689</td>
<td>6505</td>
<td>1</td>
<td>804</td>
<td>36259</td>
<td>11526</td>
<td>16124</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal Disease</td>
<td>12085</td>
<td>37151</td>
<td>20715</td>
<td>23317</td>
<td>3</td>
<td>0</td>
<td>1866</td>
<td>22673</td>
<td>18734</td>
<td>14418</td>
<td>3</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16957</td>
<td>30523</td>
<td>23880</td>
<td>24322</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td></td>
<td></td>
<td>10290†</td>
<td></td>
<td>1</td>
<td>10988</td>
<td>52023</td>
<td>36736</td>
<td>34129</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal conditions</td>
<td>25368†</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>48598</td>
<td>162699</td>
<td>93627</td>
<td>99638</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>16996</td>
<td>52213</td>
<td>29496</td>
<td>32872</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Addiction</td>
<td>53504†</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>138525</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic conditions other than diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood conditions</td>
<td>13458†</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>138525</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>All causes</td>
<td>5271</td>
<td>52341</td>
<td>17132</td>
<td>21257</td>
<td>14</td>
<td>1037</td>
<td>53793</td>
<td>16398</td>
<td>19352</td>
<td>10</td>
<td>30**</td>
</tr>
</tbody>
</table>

Costs reported in $US2015 dollars

1 Some studies included both adjusted and unadjusted costs

*Single total cost/total healthcare cost reported

** In addition to disease-specific studies of the economic impact of medication nonadherence, studies reported the all-causes costs, encompassing cost drivers such as comorbidities. Álvarez Payero et al reported all cause costs only.

- Do not report total cost/total healthcare cost
- Single total cost/total healthcare cost reported
<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td></td>
<td><strong>Title</strong> 1 Identify the report as a systematic review, meta-analysis, or both.</td>
<td></td>
</tr>
<tr>
<td>ABSTRACT</td>
<td></td>
<td><strong>Structured summary</strong> 2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td></td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
<td><strong>Rationale</strong> 3 Describe the rationale for the review in the context of what is already known.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Objectives</strong> 4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td></td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td><strong>Protocol and registration</strong> 5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<tr>
<td></td>
<td></td>
<td><strong>Eligibility criteria</strong> 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<tr>
<td></td>
<td></td>
<td><strong>Information sources</strong> 7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<tr>
<td></td>
<td></td>
<td><strong>Search</strong> 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Study selection</strong> 9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Data collection process</strong> 10 Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td></td>
</tr>
<tr>
<td></td>
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<td><strong>Data items</strong> 11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<tr>
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<td><strong>Risk of bias in individual studies</strong> 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td></td>
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<tr>
<td></td>
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<td><strong>Summary measures</strong> 13 State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<tr>
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<td><strong>Synthesis of results</strong> 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td></td>
</tr>
</tbody>
</table>
**PRISMA 2009 Checklist**

<table>
<thead>
<tr>
<th>Section/topic</th>
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<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td></td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS**

| Study selection                        | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |                    |
| Study characteristics                   | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |                    |
| Risk of bias within studies             | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |                    |
| Results of individual studies           | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |                    |
| Synthesis of results                    | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |                    |
| Risk of bias across studies             | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |                    |
| Additional analysis                     | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |                    |

**DISCUSSION**

| Summary of evidence                     | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |                    |
| Limitations                              | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |                    |
| Conclusions                              | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |                    |

**FUNDING**

| Funding                                  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |                    |


For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).